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(71) Applicant (for all designated States except US): TRANSVASCULAR, INC. [US/US]; 1505-D Adams Drive, Menlo Park, CA 94025 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): MAKOWER, Joshua [US/US]; 450 Tyndall Street, Los Altos, CA 94022 (US). LAMSON, Theodore, C. [US/US]; 2172 Camino Brazos, Pleasanton, CA 94566 (US). FLAHERTY, J., Christopher [US/US]; 242 Ipswich Road, Topsfield, MA

01983 (US). REGGIE, John, A. [US/US]; 1145 Amarillo Ave. #15, Palo Alto, CA 94303 (US). CHANG, John, Y. [US/US]; 13080 Lorene Court, Mountain View, CA 94040 (US). CANTANESE, III., Joseph [US/US]; 1963 Woodwide Road # 9, Redwood City, CA 94061 (US). THOLFSEN, David, R. [US/US]; 263 Crescent Ave, San Francisco, CA 94110 (US).

(74) Agent: BUYAN, Robert, D.; Stout, Uxa, Buyan & Mullins LLP, 4 Venture, Suite 300, Irvine, CA 92618 (US).

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(54) Title: DEVICES, SYSTEMS AND METHODS FOR ACUTE OR CHRONIC DELIVERY OF SUBSTANCES OR APPARATUS TO EXTRAVASCULAR TREATMENT SITES



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(57) Abstract: Methods and apparatus for delivery of substances or apparatus to target sites located outside blood vessels within the body of a human or animal patient. A vessel wall penetrating catheter is inserted into the vasculature, positioned and oriented within a blood vessel near the target extravascular site and a penetrator is advanced from the catheter so as to penetrate outwardly through the wall of the blood vessel in the direction of the target site. Thereafter, a delivery catheter is passed through a lumen of the penetrator to the target site. A desired substance or apparatus is then delivered to or obtained from the target site. In some applications, the penetrator may be retracted into the vessel wall penetrating catheter and the vessel wall penetrating catheter may be removed, leaving the delivery catheter in place for chronic or continuous delivery of substance(s) to and/or obtaining of information or samples from the target site. Alternatively, a delivery catheter having an occlusion member or balloon may be advanced into a vein or venule and the occlusion member or balloon may be used to occlude the lumen of the vein or venule during and after injection of a substance through the catheter, such that the substance will not be carried away by normal venous blood flow and will remain in the vein or venule for a sufficient period of time to have its intended effect (e.g. to enter adjacent tissues through capillary beds drained by that vein or venule).

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**DEVICES, SYSTEMS AND METHODS FOR ACUTE OR CHRONIC DELIVERY
OF SUBSTANCES OR APPARATUS TO EXTRAVASCULAR TREATMENT
SITES**

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Background of the Invention

There exist many situations in which it is desirable to deliver substances (e.g., drugs, biological materials, etc) or apparatus (e.g., wires, sensors, etc.) to specific locations within tissues (i.e. an "interstitial target site") of the body of a human or veterinary patient. Examples of the types of tissues wherein such target sites may be located include myocardial tissue, brain tissue or tumors.

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Some catheters and drug delivery stents of the prior art have been purportedly useable to *indirectly* deliver drugs or substances to specific interstitial target locations by first dispensing the drug *within* the lumen of a nearby blood vessel or on the inner surface of a nearby blood vessel and then allowing the drug to migrate through the blood vessel wall or through a downstream capillary bed, to the desired interstitial target location.

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The prior art has also included catheter devices that may be used for delivering substances or apparatus *directly* into interstitial target locations by guided advancement of a penetrating cannula or needle from a catheter located within the lumen of a nearby blood vessel, through the wall of the blood vessel and through any intervening tissue, to the interstitial target site. The desired substance or apparatus may then be infused or delivered directly into the target interstitial site without any need for transmural diffusion through the blood vessel wall or downstream transluminal flow to the selected capillary bed. Examples of these catheter devices useable for direct delivery of drugs or apparatus into interstitial target sites are described in PCT International Patent Publications No. PCT/US99/07115 and PCT/US99/07112.

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Particular interest has developed in methods for controlled or targeted delivery of substances such as drugs (e.g., chemotherapeutic agents), gene therapy compositions (e.g., plasmids, viral vectors, genetically modified cells, naked DNA), biological factors (e.g., angiogenic factors, nerve growth factors, other cell growth factors, other proteins), monoclonal antibodies, or specific cell types (e.g., stem cells or other progenitor cells, pancreatic islet cells, dopamine secreting

neurons, endothelial cells, myocardial cells, other myocytes, etc) into interstitial target locations for the purpose of treating diseases such as myocardial ischemia, solid tumor types of cancer, parkinsonism, diabetes, etc. Specifically, in the treatment of myocardial ischemia, research has indicated that introduction of 5 certain angiogenic substances into ischemic areas of myocardium may result in "therapeutic angiogenesis" in patients who suffer from clinically significant coronary artery disease. Generally speaking, the term "angiogenesis" refers to the creation of new capillaries and/or blood vessels within the parenchyma of an organ, within a tumor or within an area of tissue (e.g., myocardium). Angiogenesis is believed 10 to occur as a multistep process in which endothelial cells focally degrade and invade through their own basement membrane, migrate through interstitial stroma toward an angiogenic stimulus, proliferate proximal to the migrating tip, organize into blood vessels, and reattach to newly synthesized basement membrane. The term "therapeutic angiogenesis" involves the administration of angiogenic 15 substances or treatments to promote one or more steps in the angiogenesis process thereby providing for the creation of new blood flow in tissue that previously lacked sufficient blood flow.

Various approaches have heretofore been used for delivery of angiogenic substances into the myocardium. One approach is the use a tissue penetrating 20 device such as a laser to create penetration tracts or transmyocardial (TMR) channels which extend from either the epicardial (outer) surface or endocardial (inner) surface of the heart into the myocardium, and to then inject quantities of angiogenic substances into those TMR channels. Examples of this approach are described in United States Patent Nos. 5,925,012 (Murphy-Chutorian, et al.), 25 5,999,678 (Murphy-Chutorian, et al.) And 6,106,520 (Laufer, et al.)

There remains a need in the art for the development of new apparatus and methods for delivering substances or apparatus to specific target sites within tissues, tumors or organs of the body with minimal trauma to the tissues and optimum control as to the precise location(s) at which the substances or apparatus 30 are introduced.

Summary of the Invention

The present invention provides transluminal methods, devices and systems for delivering substances (e.g., drugs or other therapeutic or diagnostic agents) or articles (e.g., devices, apparatus, wires, sensors, thermistors, etc.) to interstitial sites within the body of a human or veterinary patient.

In accordance with one aspect of the invention, there is provided a system comprising a) a penetrating catheter that is positionable within the vasculature (e.g., a blood vessel, vascular sinus or chamber of the heart) of a human or animal patient and which has a penetrator advanceable from the catheter in the direction of an extravascular target site and b) a delivery catheter that is advanceable from the penetrator to the target site. As used herein, the term "vessel wall" shall mean not only the wall of a blood vessel (i.e., artery or vein) but also the endocardium surrounding a chamber of the heart or any other wall of an anatomical structure in which the penetrating catheter is positioned and through which the penetrator advances to reach its intended position within adjacent tissue. The Substance(s), article(s) or apparatus may then be delivered to the target site through the delivery catheter and/or samples of body fluid or other information may be obtained from the target site through the delivery catheter. In applications where it is desired to use the delivery catheter continuously or intermittently over an extended period of time (e.g., hours, days, weeks or months) the penetrator may be withdrawn into the vessel wall penetrating catheter and the vessel wall penetrating catheter may be removed, leaving just the delivery catheter in place (e.g., extending through the patients blood vessel(s), outwardly through the penetration formed in the blood vessel wall and to the target site.) Also, the substance or article(s) may be injected periodically or continuously as the delivery catheter is being advanced or retracted, so as to provide a continuous "trail" or series of deposition sites wherein the substance or article(s) is/are deposited.

In accordance with the invention, the use of a unicurvate or multicurvate penetrator (or a curved delivery catheter in combination with a straight, unicurvate or multicurvate penetrator) may serve to guide the delivery catheter on a path that is navigates around anatomical structures or avoid penetration into a cavity, organ

or anatomical structure that the operator does not wish for the delivery catheter to enter. In this regard, the delivery catheter may be guided such that it advances on a path that is generally tangential to the wall or edge or a chamber of the heart or other cavity or anatomical structure that the operator does not wish to enter or 5 penetrate. This ability to avoid penetration of a chamber, cavity or anatomical structure may allow a greater length of the delivery catheter to be advanced into the tissue than would have been otherwise possible. The advancement of a greater length of delivery catheter into the tissue may allow for deposition of a longer trail or a more lengthy series of depots of an injected material than would be possible 10 if the delivery catheter were to have been advanced in the direction of or non-tangentially to the chamber of the heart or other cavity or anatomical structure that the operator does not wish to enter or penetrate. Also, the ability to provide a lengthy trail or series of deposition sites may be advantageous in certain 15 applications of the invention. For example, the ability to deposit a tissue graft or cells (e.g., stem cells, myoblasts, etc.) in an elongate trail may allow for the cells to form an organized structure wherein the cells communicate with one another and/or form a connection between two spaced apart regions of an organ or tissue mass. In cases where angiogenic substances are being injected through the delivery 20 catheter, the ability to lay down a trail of the angiogenic substance may permit the operator to define a line or elongate region of new blood vessel growth. Also, advancement of a more lengthy segment of the delivery catheter into the tissue may provide for deeper injection of substances with less potential for bleedback or 25 regurgitation through the interstitial tract created by advancement of the penetrator and/or delivery catheter. Also, this capability of the system allows for the deposition of a series or network of elongate trails or tracts of a substance or article, or spaced apart interstitial deposits of a substance or article in a manner that allows the individual trails, tracts or deposits to form a network and to interact with one another in a desired manner.

The types of substances that may be delivered through the delivery catheter 30 include drugs (thrombolytics, platelet inhibitors, anti-restenotic agents, beta blockers, ion channel antagonists, positive or negative ionotropic agents, anti-arrhythmics, antibiotics, analgesics, chemotherapeutic agents, other anti-neoplastic

agents, etc.), natural or recombinant proteins (e.g., angiogenic proteins such as vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF) nerve cell growth factor (NGF) or hepatocyte growth factor (HGF)), cells or cellular preparations (e.g., stem cells, other progenitor cells, myocytes, myoblasts, pancreatic islet cells, dopamine secreting cells, etc), genes or gene therapy preparations (e.g., viral vectors containing genes for gene therapy applications, genetic material for electrophoretic transmission into cells, plasmids, viral vectors, genetically modified cells, naked DNA, etc.), contrast media or dyes for imaging, 5 radio-labeled diagnostic materials or drugs or other traceable substances, mixtures of any of the above, alone, in solution or in combination with any delivery substance or matrix (e.g., polymer matrices used to inhibit or slow distribution or dissemination of a substance away from its original injection site), dialysis solutions or micro-dialysis solutions, or any other type of substances that may be introduced 10 through the delivery catheter for any therapeutic, imaging, diagnostic or other purpose.

Further in accordance with the invention, the types of target tissues into which the delivery catheter of the above-described system may be placed include various organs (e.g., heart, brain, liver, pancreas), the walls of blood vessels (by 20 injection directly into the vessel wall or by injection into a periadventitial area outside of but close to the vessel so that the drug or substance will be distributed into the vessel wall), muscles (e.g., myocardium, skeletal muscle) or aberrant masses (e.g., tumors, cysts).

Still further in accordance with the invention, substances delivered through 25 the delivery catheter may be of increased viscosity to deter their egress from the target area, may be adherent to tissues in the target area so as to deter egress of the substance from the target area and/or may harden or form a mass in situ after injection into the target area, thereby deterring egress of the substance from the target area.

30 Still further in accordance with the invention, the outlet port(s) of the delivery catheter may be configured such that substances injected through the

delivery catheter will form high pressure jet sprays into the tissue surrounding the delivery catheter.

Still further in accordance with the invention, the vessel wall penetrator of the vessel wall penetrating catheter and/or the delivery catheter may be equipped with 5 backflow deterrent for limiting or preventing fluid that is injected through the delivery catheter from bleeding back through the tissue tract through which the delivery catheter and/or penetrator was/were advanced. In chronic dosing applications wherein the delivery catheter remains indwelling, such backflow deterrent may comprise a balloon, annular rib or other barrier formed on the outer surface of the 10 delivery catheter to block the backflow of fluid through the tract in which the delivery catheter resides. In acute dosing applications wherein the delivery catheter is extracted and removed immediately after injection of the substance, the backflow deterrent may comprise a) an embolizing member such as a detachable blocker, balloon, clot, fibrin, bead of polyvinyl alcohol, etc. that is deployed into the tissue 15 tract as the delivery catheter and/or penetrator is/are retracted, b) a substance such as a cyanoacrylate, polyethylene glycol, hydrogel, fibrin glue or other material is injected to embolize, seal or close the tract through which the delivery catheter and/or penetrator was/were advanced or c) a tissue fusing device, such as a radio-frequency emitting electrode, for welding or fusing adjacent tissue in a way that 20 effectively closes the tract through which the delivery catheter and/or penetrator was/were advanced.

Still further in accordance with the invention, the delivery catheter of the above-described system may be used for aspiration of samples of blood or body fluid from the target site and/or may include one or more interactive members, such 25 as emitters, detectors, electrodes, sensors, etc. for a) facilitating the delivery catheter's penetration through tissue, b) facilitating the distribution of an injected substance into surrounding tissues (e.g., by iontophoresis), c) creating a pocket into which a substance may be injected or d) sensing the position of the delivery catheter or some content or variable (e.g.,ECG, contractility, force of contraction, 30 pressure, local ECG amplitude, local protein levels, local antibody levels, pO_2 , pCO_2 , oxygen saturation, blood flow rate, pH, local lactate levels, etc.) of the adjacent tissue.

Still further in accordance with the invention, the delivery catheter may be used to continuously or intermittently monitor physiological parameters or variables (e.g., rate of blood flow away from the site) or pharmacokinetic or biodistributive parameters or variables (e.g., the rate at which a substance will distribute away from the target site, how long the injected substance may be expected to remain at the target site, the rate at which the injected substance may be inactivated or metabolized at the target site and/or other parameters/variables relating to the activity of the substance after it has been injected at the site). Such information may then be used to verify that the delivery catheter is suitably placed for optimal or desired therapeutic effect of an injected substance or apparatus delivered to the site. If it is determined that an injected substance is likely to distribute away from the target site too quickly, or remain at the target site for too long, or become inactivated too quickly or not quickly enough, the delivery catheter may be repositioned to a site that is more desirable. Similarly, if it is determined that the site is too vascularized or not vascularized enough for the desired therapeutic or diagnostic activity of the delivered substance or apparatus, the delivery catheter may be repositioned to a new target site that is suitably vascularized, before continuing with delivery of the substance or apparatus through the delivery catheter. One example of a manner in which this type of site monitoring may be accomplished is to deliver radio-opaque dye, a radio-labeled substance or other traceable material through the delivery catheter and to the location adjacent the outlet port(s) of the delivery catheter (i.e., the target site to which the therapeutic or diagnostic substance is being or will be delivered) Thereafter, the rate at which that traceable substance distributes away from that site (or the rate at which it becomes inactivated, degraded or metabolized) may be measured by appropriate means such as x-ray (when radio-opaque traceable material is used) or radio-scanning (when radio-labeled traceable material is used). If the site is deemed to be acceptable, the therapeutic or diagnostic substance or apparatus may be delivered to the site. If the site is deemed to be unacceptable (or less than optimal) the delivery catheter may be repositioned and the test may be repeated. In some applications, the delivery catheter may have multiple lumens such that a therapeutic or diagnostic substance or apparatus may be delivered through one lumen and a

traceable substance useable for site monitoring/verification may be delivered through another lumen.

Still further in accordance with the invention, the delivery catheter of the above-described system may include anti-obstruction apparatus (e.g., a mandrel, stylet, inflatable member or semi-permeable barrier) that allows the desired substances or apparatus to be introduced in the distal direction through the delivery catheter but prevents cellular ingrowth or other matter from invading and obstructing the lumen and/or outlet port(s) of the delivery catheter. In this manner, the delivery catheter remains patent, even when it has been indwelling within tissue for an extended period of weeks or months.

Still further in accordance with the invention, the efficacy of substances injected through the delivery catheter may in some applications be enhanced by limiting the rate at which the substance distributes away from the site or otherwise altering the biodistribution and/or pharmacokinetics of the substance after it has been introduced into the body. This may be accomplished by introducing the substance in the form of a solid, dry pellet, implant, filament or gel. Alternatively, this may be accomplished by micro-encapsulating or mixing the substance with a polymer matrix, oil or other drug delivery matrix or material that is prepared before injection or formed *in situ* or by forming liposomes or colloidal suspensions containing the substance, etc. Another way in which this may be achieved is by causing the substance to promptly enter cells rather than allowing the substance to remain disposed in intercellular fluids or intercellular spaces from which the substance may quickly distribute or disseminate away from the injection site (e.g., by driving the substance into adjacent cells by electrophoretic means or chemical means, by modifying the properties (e.g., solubility, polarity, pH) of the substance in a manner which will facilitate its transport into cells, by atomizing or spraying the substance as it exits the catheter, or by causing the substance to exit the catheter at increased velocity or force).

The invention together with additional features and advantages thereof may best be understood by reference to the following description taken in connection with the accompanying illustrated drawings.

Brief Description of the Drawings

Figure 1 is a schematic showing of a human patient who is undergoing a procedure for transvenous placement of a delivery cannula for ongoing delivery of drugs or apparatus to an ischemic region of the patient's myocardium.

5 Figure 2 is a broken, side view of one embodiment of a catheter system of the present invention.

Figure 2a is an enlarged, cut-away view of section 2a of Figure 2.

Figures 2b-2d show, in step-by-step fashion, the manner in which the catheter system of Figure 2 may be used to accomplish transluminal placement of 10 a delivery catheter for delivery of substances or apparatus to an extravascular target location.

Figure 3a shows an embodiment of a delivery catheter of the present invention which incorporates a subcutaneous injection port for periodic infusion of fluids through the delivery catheter.

15 Figure 3b shows an embodiment of a delivery catheter of the present invention which incorporates an exteriorized Luer fitting for attachment of a syringe to the delivery catheter for periodic infusion of fluids through the delivery catheter.

Figure 4 is a partial perspective view of a delivery catheter of the present invention having a plurality of side apertures for disseminated outflow of fluid 20 therefrom and a balloon for preventing injected fluid from backflowing through the tract through which the delivery catheter extends.

Figure 5 is a partial perspective view of a delivery catheter of the present invention having a plurality of side apertures for disseminated outflow of fluid therefrom and a stylet member that is insertable into the lumen of the delivery 25 catheter to block the side apertures at times when no fluid is being infused through the delivery catheter.

Figure 6a is a partial perspective view of a delivery catheter of the present invention having a plurality of side apertures for disseminated outflow of fluid therefrom and any inflatable obturator position within the lumen of the delivery 30 catheter in an inflated state wherein the obturator blocks the side apertures at times when no fluid is being infused through the delivery catheter.

Figure 6b is a partial perspective view of the delivery catheter of Figure 6 wherein the obturator is in a deflated state such that fluid may be infused through the lumen of the delivery catheter and out of the side apertures.

Figure 7 is a partial longitudinal sectional view of a delivery catheter the 5 present invention having a plurality of side aperture is for disseminated outflow of fluid therefrom and a semi-permeable diffusion barrier mounted about the catheter such that fluid infused through the lumen of the delivery catheter and out of the side apertures will collect within the diffusion barrier and will subsequently diffuse outwardly through the barrier while the diffusion barrier prevents cellular matter or 10 other material from invading and obstructing the side apertures or lumen of the delivery catheter.

Figure 8a is a partial longitudinal sectional view of a delivery catheter the present invention having an open distal end and a spring mounted tip member having a fluid outlet channel formed therein, such tip member being in a retracted 15 position wherein the fluid outlet channel is fully covered by the catheter body and cellular matter or other material is prevented from invading and obstructing the fluid outlet channel.

Figure 8b is a partial longitudinal sectional view of the delivery catheter of Figure 8a, wherein fluid is being infused in the distal direction through the lumen of 20 the delivery catheter and the pressure of the fluid has advanced the distal tip member to an extended position wherein the fluid outlet channel uncovered and fluid is permitted to flow from the lumen of the delivery catheter, outwardly through the fluid outlet channel.

Figure 9a is a partial perspective view of a delivery catheter the present 25 invention having an open distal end and a coil spring mounted tip member mounted thereon, such tip member being in a retracted position wherein the convolutions of the coil spring are contracted into abutting contact with each other, thereby closing the lumen of the delivery catheter and preventing cellular matter or other material from invading and obstructing the lumen of the delivery catheter.

30 Figure 9b is a partial perspective view of the delivery catheter of Figure 9a wherein fluid is being infused in the distal direction through the lumen of the delivery catheter and the pressure of the fluid has advanced the distal tip member to an

extended position wherein the convolutions of the coil spring are spaced apart and fluid is permitted to flow from the lumen of the delivery catheter, outwardly through the spaces between the convolutions of the coil spring.

5 Figure 10 is a diagram of a human heart showing the manner in which a delivery catheter of the present invention may be transvenously implanted within an interstitial target site of the myocardium.

10 Figure 10a is an enlarged, cut-away view of a portion of Figure 10, showing the manner in which the delivery catheter extends through the wall of a coronary vein and in generally tangential relationship to the adjacent left ventricle of the heart.

15 Figure 11 is a diagram of a human heart showing the manner in which a delivery catheter of the present invention having a backflow preventing balloon thereon may be positioned within a coronary vein to deliver a substance to a target region of the myocardium by selective, retrograde infusion through the coronary vein.

20 Figure 12 is an enlarged, cut-away view of a portion of Figure 11, showing the backflow preventing balloon in an inflated state and a substance being infused through the delivery catheter and through the coronary vein in the retrograde direction.

25 Figure 13 is a partial, side view of a vessel wall penetrating catheter of the present invention showing the varying angles at which the vessel wall penetrating member may be deployed, relative to the longitudinal axis of the catheter body, depending on the extent to which the vessel wall penetrating member has been advanced.

30 Figure 14 is a partial perspective view of another tissue penetrating catheter system of the present invention.

Figure 15 is a diagram of the catheter system of Figure 14 positioned within a chamber of a human heart and being used to deliver a substance into the myocardial wall via an endocardial approach.

35 Figure 16 is a diagram of a modified catheter system of Figure 14 having a corkscrew penetrator positioned within a chamber of a human heart and being used to deliver a substance into the myocardial wall via an endocardial approach.

Figure 16a is a schematic diagram illustrating the manner in which the catheter system of Figure 16 may be used to deposit a series or radially arranged elongate tracts or trails of a substance within a mass of tissue creating a "wagon wheel" pattern of substance deposition within the tissue.

5 Figure 17 is a diagram of a catheter system comprising a tissue penetrating catheter having a laterally deployable penetrator combination with an optional guide catheter, positioned within a chamber of a human heart and being used to deliver a substance into the myocardial wall via an endocardial approach.

10 Figure 18 is a perspective view of a human heart having an area of necrotic myocardium due to a prior infarct, wherein a penetrating catheter of the present invention has been advanced into a coronary vein and the penetrator and delivery catheter are being used to deliver a therapeutic substance into the necrotic area of myocardium.

15 Figure 18a is an enlarged view of region 18a of Figure 18.

Figure 19 is a cross sectional view through line 19-19 of Figure 18.

Detailed Description of Preferred Embodiments

20 The following detailed description, and the drawings to which it refers, are provided for the purpose of describing and illustrating certain examples or embodiments of the invention only and are not intended to exhaustively describe or show all possible embodiments or examples of the invention.

25 Generally, one method of the present invention may be carried out by first inserting a vessel wall penetrating catheter into the vasculature of a human or veterinary patient, advancing the vessel wall penetrating catheter through the vasculature to a location within a blood vessel that is adjacent or near a target location at which a substance (e.g. a drug, biological or therapeutic agent) or apparatus (e.g. a sensor) is to be delivered and thereafter advancing a vessel wall penetrator from the catheter, transmurally through the wall of the blood vessel, in the direction of the target location. In some embodiments, the vessel wall penetrator itself may comprise a tubular member through which a substance or apparatus may be passed. In those embodiments, the penetrator will be advanced all the way to the target location(s) and the substance or apparatus will then be

infused or delivered through the lumen of the penetrator. In other embodiments, a separate delivery catheter will be advanced through the vessel wall penetrator to the target location and, thereafter, the vessel wall penetrator may be withdrawn and removed (along with the entire vessel wall penetrating catheter) leaving only 5 the delivery catheter in place. This secondary catheter may then remain indwelling for whatever period of time is desired, to allow samples to be withdrawn from the target location or to allow therapeutic agents and/or apparatus (e.g. wires or sensors) to be introduced to the target location at desired intervals or on a desired schedule.

10 **A. *Transluminally Deployable Catheter System for Acute or Chronic Delivery of Substances or Apparatus to Interstitial Target Sites:***

15 Figures 2-2d show an example of a catheter system 10 of the present invention. This system 10 comprises the combination of a vessel wall penetrating catheter 11 and a delivery catheter 12. Figure 1 shows this catheter system 10 in use on a human patient.

Vessel Wall Penetrating Catheter

20 In the embodiment illustrated, the vessel wall penetrating catheter 11 includes an elongated catheter body 13 having a proximal end 15, a distal end 17, a handle 19 and a hub 21 coupled to the proximal end of the catheter body and to the handle. The handle 19 may also serve as a controller for use in advancing and 25 retracting the vessel wall penetrator 85, as described more fully below.

25 The vessel wall penetrating catheter body 13 includes a relatively rigid proximal section 23 shown in Figs. 2 and 3a which may be constructed, for example, of a metal hypo tube and an elongated flexible distal section or region 25 suitably joined to the proximal section. At least the distal section 25 is sized to be received within a coronary artery, and therefore can be received within either a coronary artery or a coronary vein. The catheter body section 13 has a penetrator lumen 27 which terminates distally at an exit location or exit port 29 that is located on a peripheral wall 31 of the catheter body. A vessel wall penetrator 85, such as 30 a hollow NiTi needle as shown in Figures 2a (phantom lines), 2b and 2c, is disposed within the penetrator lumen 27 and is advanceable out of the side exit port 29 as seen in Figures 2a-2c. The exit port 29 is preferably located a short distance

proximally of the distal end 17. A radiopaque marker 33 may be mounted on the lumen 27 adjacent the exit port 29 to facilitate placement and positioning of the vessel wall penetrating catheter 11. The penetrator 85 may be a single hollow member or may consist of a series of hollow members which advance through one another or telescope in a desired manner. In embodiments where the penetrator consists of a plurality of hollow members which advance through one another or telescope, the individual members may have differing curvatures or differing shapes to allow the penetrator or follow a multicurvate path of advancement. This may be useful in applications where the penetrator is required to advance around a prohibited zone or anatomical structure that the operator does not wish to penetrate.

The catheter body 13 also has a guidewire lumen 35 (Fig. 3a) which extends to the distal end 17 of the catheter body 15. In this embodiment, the guidewire lumen 35 extends proximally to an inlet port 37 at the peripheral wall 31 closely adjacent the proximal section 23.

A major section 51 of the catheter body 13 terminates distally in a distal opening 53, and the catheter body includes a distal tip section 55 of soft, flexible, biocompatible material (Figs. 3a and 3b). A proximal portion 56 of the distal tip section 55 is received in the distal opening 53 and a distal portion of the distal tip section 55 extends distally to the distal end 17. The distal portion of the distal tip section 55, i.e. the portion of the distal tip section 55 which extends beyond the distal end of the major section 51 is of smaller cross sectional area than the adjacent-region-of-the-major-section-to-thereby-define-an-annular-shoulder 57 on the catheter body 13. The exit port 29 is spaced slightly proximally of the shoulder 57.

Guidance Elements

In many embodiments, it will be desirable for the vessel wall penetrating catheter 11 to include a guidance element for guiding the positioning and rotational orientation of the catheter 11 within the vasculature such that the vessel wall penetrator 85 will be properly aimed in the direction of the target site. Such guidance element may include marker(s), imaging apparatus, emitter(s), sensor(s)

etc. In the particular embodiment shown in figures 2a and 2b, the guidance element comprises the combination of an imaging transducer 81 and an imageable marker assembly 101. The imaging transducer 81 is fixedly mounted on the catheter 11, and in the embodiment illustrated in Fig. 3a, the imaging transducer 5 is mounted on the distal tip section 55 just distally of the shoulder 57. In this embodiment, the imaging transducer 81 is a phased array transducer and is operative to image 360° about the vessel wall catheter 11. The imaging transducer 81 is coupled to a multiplex circuit 83 which is within the major section 51 of the catheter body 13 adjacent the shoulder 57, and the multiplex circuit 83 is in turn 10 coupled to leads 85 which extend through the lead lumen 39, through the handpeice 19 and are attached to a connector 86 which allows the leads 39 to be connected to a viewing instrument and screen. When activated, the imaging transducer emits ultrasound signals and receives back echos or reflections which are representative of the nature of the surrounding environment. The imaging 15 transducer provides an imaging signal from which an image of the surrounding structure can be created on a screen of the viewing instrument. In a preferred practice of this invention, the phased array transducer, the accompanying circuitry and the separate viewing instrument/screen may be obtained from Endosonics, Inc. of Rancho Cordova, California.

20 In an alternate embodiment of this invention, the imaging element may be formed of a single rotating crystal or transducer. In this embodiment the transducer would have a single lead out, would include a drive shaft which would run back to the proximal end of the catheter through 39.

25 In the particular embodiment shown, an imageable marker 101 is fixedly mounted on the catheter body 13 in a known circumferential orientation relative to the exit port 29. This marker 101 may be in the form of a structure or cage, as shown, and the transducer 81 may be located within the marker cage or marker structure. In the embodiment shown, the marker cage comprises a plurality of longitudinal members 103 disposed at circumferentially spaced apart locations 30 about a hollow interior space 105. The hollow space 105 receives the distal tip section 55 and the transducer 81, and the transducer 81 is an onboard transducer in that it is inseparable from and not removable from the catheter body 13. One of

the longitudinal members is located at a circumferential position that is axially aligned with the exit port 29 and consequently is also axially aligned with the path that will be followed by a tissue penetrator that is advanced from the catheter body 13 through the exit port. Thus, the imageable marker 101 forms on the image 5 obtainable from the imaging signal from the imaging transducer a penetrator path indication that indicates the path that will be followed by the tissue penetrator when the tissue penetrator is advanced from the catheter. As an alternative to the use of a marker 101, the path that will be followed by the penetrator may be indicated on the image by electronic means or by the use of a computer program, thereby 10 eliminating the need for a penetrator path indicating marker 101. In many embodiments, the marker 101, electronic penetrator path indicator or computer program for determination of the penetrator path may not only indicate the trajectory or path of the penetrator but may also indicate a stopping point at which advancement of the penetrator will stop or is intended to stop. By providing such 15 an indication of the mandatory or intended stopping point of the penetrator advancement, the operator may cause the penetrator to be optimally positioned at the intended site without advancing the penetrator too far as may result in missing of the intended delivery site or unwanted penetration of a blood vessel or other anatomical structure that lies beyond the site at which the penetrator is desired to 20 stop.

With the construction described above, the imaging transducer 81 and the marker 101 are both mounted on the distal tip section 55 which has a smaller cross 25 sectional area than does the adjacent region of the major section 51 of the catheter body 13. Accordingly, the cross sectional area of the catheter body 13 at the region containing the imaging transducer 81 and the marker 101 can still be relatively small. Also, the exit location 29 is closely adjacent to the imaging transducer 81 and may be, for example, about 5 mm from the imaging transducer. This minimizes the likelihood of any significant torsional displacement of the exit location 29 relative to 30 the marker 101 and imaging transducer 89. It may also be appreciated that the imaging transducer may be mounted such that the exit port is located directly at the point at which the transducer is affixed to the catheter, illuminating any displacement.

It will be appreciated that various other types of imaging or position sensing apparatus may be used as alternatives to the above-described imaging transducer 89/marker 101 combination to guide and orient the vessel wall penetrating catheter 11. For example, the vessel wall penetrating catheter 11 may incorporate an 5 emitter that is useable in conjunction with an electromagnetic, potentiometric, or other electro-anatomical mapping and/or catheter guidance/positioning systems, such as those commercially available from or under development by Biosense Webster, Inc., Diamond Bar, California; Cardiac Pathways Corporation, 995 Benicia Avenue, Sunnyvale, CA and/or Stereotaxis, Inc., 4041 Forrest Park Avenue, St. 10 Louis, MO. Examples of these types of catheter guidance or positioning systems are described in United States Patent Nos. 5,820,568 (Willis), 5,931,818 (Werp et al.), 5,654,864 (Ritter et al.), 5,928,248 (Acker), 5,752,513 (Acker et al.), 5,558,091 (Acker et al.) And 5,833,608 (Acker), the entire disclosures of which are expressly incorporated herein by reference.

15 Delivery Catheter

After the vessel wall penetrator 85 has been advanced to the desired extended position, the delivery catheter 12 may be advanced through the lumen of the penetrator 85 and out of its distal end. For applications where it is desired for the delivery catheter 12 to penetrate into myocardial tissue, the delivery catheter 20 12 may comprise a small cannula, hypotube or microcatheter formed of a suitable material such as polyimid, polytetrafluoroethylene, polypropylene, polyethylene, Pebax™, etc. For many applications, including application wherein the delivery catheter 12 is used to deliver substances into the myocardium, the delivery catheter 12 may have an outer diameter of approximately 0.25-0.5 mm. In embodiments 25 where it is intended for the delivery catheter to penetrate through tissue as it advances the distal tip of the delivery catheter 12 may be beveled or sharpened. Optionally, the delivery catheter 12 may have an energy emitting distal tip for enhanced tissue penetrating capability. For example, a radiofrequency electrode may be located on or near the distal tip of the delivery catheter to provide for tissue 30 penetration enhanced by RF energy emission. Or, the delivery catheter may be adapted to ultrasonically vibrate, thereby improving its ability to penetrate through tissue.

The body of the delivery catheter 12 may be radio-opaque or one or more radio-opaque markers may be formed on the delivery catheter (e.g., at its distal tip) to permit imaging of the catheter and determination of the position of the catheter within the patient's body.

5 In some applications, such as those where drugs, substances or apparatus are to be chronically delivered to the target site over a period of days, weeks or months, the delivery catheter will be allowed to remain indwelling after the vessel wall penetrating catheter 11 has been removed. To facilitate this, a detachable or removable Luer connector 47 may mountable proximal end of the delivery catheter
10 12 as shown in Figures 2 and 3b. This detachable or removable Luer connector may be removed when during proximal withdrawal and removal of the vessel penetrating catheter 11 while the delivery catheter 12 remains in place. Thereafter, in embodiments wherein the proximal end of the delivery catheter 12 remains exteriorized, the removable or detachable Luer connector 47 may be attached to
15 the exteriorized proximal end of the delivery catheter 12 and may thereafter be used for subsequent attachment of a stopcock 47 and/or syringe 50 as shown in Figure 3b. In other embodiments, the proximal end of the delivery catheter 12 may be devoid of any hub or connector and may be connected to a pump, delivery device, subcutaneously implanted reservoir or injection port 52, as shown in Figure
20 3a.

An opening for infusion or aspiration of substances/apparatus may be formed in the distal end of the delivery catheter 12 and/or one or more fluid outlet openings may be formed in the sidewall of the delivery catheter 12, near its distal end, as shown in figures 2c or 2d. For many applications, one or more openings
25 may be laser drilled into the delivery catheter 12, such openings being no more than $\frac{1}{2}$ the diameter of the catheter lumen through which the substance is being injected, such that high pressure jets of the substance will be created as the substance exits the delivery catheter 12. The creation of such elevated pressure as the substance exits the delivery catheter 12 serves to propel or drive the substance through cell membranes and into intracellular spaces cells rather than
30 allowing the substance to remain in intercellular spaces (i.e., spaces or fluids

between cells or outside of the cells) from which the substance would more rapidly distribute away from the injection site.

The delivery catheter may be straight or curved, as needed to accomplish the desired procedure. In some but not necessarily all cases, the delivery catheter 5 may constitute a very small diameter catheter of a type known in the art as a microcatheter.

Interactive Apparatus on Delivery Catheter

As shown in Figure 2c, one or more interactive members 52 such as sensors, emitters, etc. may be positioned on or near the distal end of the delivery catheter 12 for emitting energy as described above or for sensing, sampling or receiving information from the tissues adjacent the distal portion of the delivery catheter 12. Interactive members that comprise sensor(s) may provide information on the position of the delivery catheter 12 or measurements of variables such as ECG, contractility, force of contraction, pressure, local ECG amplitude, local protein 10 levels, local antibody levels, pO_2 , pCO_2 , oxygen saturation, blood flow rate, pH, local lactate levels, etc. By use of such information received from the target site, the clinician may assess or characterize the target site to ascertain its suitability 15 before introducing a substance or apparatus into the target site.

In applications where it is desired to facilitate the passage or distribution of 20 an injected substance into the surrounding tissue, the interactive member 52 may emit some facilitating energy, such as an electromagnetic field for iontophoretic transmission of the substance through the adjacent tissue.

In other applications, the interactive member 52 may emit energy, such as 25 radiofrequency energy, that will create a pocket in the surrounding tissue such that a substance or apparatus may be introduced into that pocket. The walls of the pocket may be seared by the energy so as to slow the distribution of the substance out of the pocket.

In other applications, the interactive member 52 may emit energy, such as 30 ultrasound, that facilitates distribution of a substance by permeating cell membranes or by vibrating the catheter tip.

Apertures for High Pressure Injection from Delivery Catheter

As shown in Figures 2c and 2d, the distal end of the delivery catheter may be closed and a plurality of small side apertures 24 may be formed in the sidewall 5 of the delivery catheter 12 to provide for high pressure outflow of fluid from the delivery catheter and into the surrounding tissues.

Backflow Deterrent Apparatus on Delivery Catheter and/or Penetrator

In some applications, the injection of fluids through the delivery catheter 12 into a closely confined space or interstitial site may result in some regurgitation or 10 backflow of the injected fluid through the tract through which the vessel wall penetrator 85 and/or delivery catheter 12 were advanced. In acute dosing situations where the delivery catheter is removed immediately after the dose, this backflow of the injected fluid may be prevented by sealing the penetration tract or by introducing a material (e.g., an adhesive or embolizing material) into the tract 15 during immediately after removal of the catheter 12. This may be accomplished by injecting a suitable adhesive or embolizing material such as a cyanoacrylate, polyethylene glycol, hydrogel, fibrin glue through the delivery catheter lumen as the delivery catheter 12 is being pulled back through the tissue tract through which it was initially inserted. In other applications where the delivery catheter 12 remains 20 indwelling, the backflow of fluid may be accomplished by a backflow barrier 22 (see Figure 4) such as an annular rib or inflatable balloon formed on the shaft of the delivery catheter 12 near its distal end so as to block backflow of fluid around the catheter shaft or alternatively by causing the fluid to solidify or become gelatinous such that it can not backflow through the penetration tract. Such gelling or 25 solidification of the injected fluid may be accomplished by subsequent injection or pre-mixing of the fluid with an oil, a gelatinous polymer carrier or reactant that will cause the desired thickening or solidification of the injected fluid.

Anti-Obstruction Apparatus for Maintaining Patency of Delivery Catheter

In some embodiments, especially those in which the delivery catheter 12 is 30 allowed to remain indwelling for chronic delivery of substances or apparatus to the target site, the delivery catheter may incorporate anti-obstruction apparatus that will prevent cellular ingrowth or other matter from obstructing the lumen or outflow

port(s) of the delivery catheter 12. Examples of such anti-blocking apparatus are shown in Figures 5-7.

In the embodiment of Figure 5, the delivery catheter has a closed distal end 28 and a plurality of side outlet apertures 24. A solid stylet 26 is insertable through the lumen of the delivery catheter and the outer diameter of the stylet 26 is approximately the same as the inner diameter of the delivery catheter such that, when inserted, the stylet 26 will substantially close-off or block the side apertures 24 thereby preventing cellular ingrowth or other matter from entering the side apertures 24 or lumen of the delivery catheter. Thus, the stylet 26 may be inserted into the delivery catheter at times when no fluids or other substances are being infused, but may be removed at appropriate times to allow the desired infusions of fluids or other substances through the delivery catheter.

In an alternative variation of the embodiment shown in Figure 5, the stylet 26 could have a lumen which extends longitudinally through the stylet to a closed distal end and side aperture(s) or slot(s) or other opening(s) could be formed in the stylet so as to be alignable with the side apertures 24 of the delivery catheter. In such embodiment, the stylet would be maintained in one position when it is desired to block the side apertures 24 to prevent cellular ingrowth or other matter from entering the side aperture's or lumen of the delivery catheter but may be rotated or otherwise moved to a second position wherein the aperture(s), slot(s) or other opening(s) of the stylet 26 would become aligned with the side aperture's 24 of the delivery catheter such that fluid may be injected through the lumen of the stylet and outwardly through the side apertures of the delivery catheter 24. Thereafter, when the fluid injection has been completed, the stylet could be once again rotated or otherwise moved to the first position to once again close-off or block the side apertures 24 of the delivery catheter.

Figures 6a and 6b show another embodiment wherein the delivery catheter has a closed distal end 28 and a plurality of side outlet apertures 24. In this embodiment, an inflatable obturator 30 is disposed within the lumen of the delivery catheter. When the obturator 30 is inflated, as shown in Figure 6a, it will close-off or block the side apertures 24 thereby preventing cellular ingrowth or other matter from entering the side apertures 24 or lumen of the delivery catheter. However,

when the obturator 30 is deflated, as shown in Figure 6b, fluids may be infused in the distal direction through the lumen of the delivery catheter and out of the side apertures 24.

In the embodiment of Figure 7, a semi-permeable diffusion barrier 58 is 5 mounted about the outer surface of the delivery catheter so as to cover the catheter's side apertures 24. This diffusion barrier 58 is in the nature of a balloon and is formed of material that permits the substances or fluids injected through the catheter to diffuse outwardly through the barrier 58, but also prevents cellular ingrowth or other matter from invading the interior of the barrier 58 and entering the 10 side apertures 24 or lumen of the delivery catheter. The desired semi-permeability of the diffusion barrier 58 may be a function of the size of pores or openings in the barrier or balloon 24. Thus, polymer films having appropriately sized pores may be used to form the diffusion barrier 58. One polymer material that may be used in film form to create the diffusion barrier 58 is commercially available as NutraporeTM from 15 Anamed, Inc., 1 Technology Drive, Bldg. D-409, Irvine, CA 92618.

Figures 8a and 8b show another embodiment of a delivery catheter 12 having its opened distal end and a spring-mounted tip member 42 disposed within the distal end of the catheter 12. The tip member 42 has a fluid flow channel 44 that extends through the tip member 42 and opens through the side of the tip 20 member 42, as shown. The tip member 42 is attached to the catheter 12 by way of a spring 40. The spring 40 is biased to a contracted position as shown in Figure 8a, wherein the tip member 42 is drawn into the lumen of the catheter 12 such that the side opening of the fluid flow channel 44 is covered by the wall of the catheter 12 and cellular ingrowth or other matter is thereby prevented from entering the fluid 25 flow channel 44 or lumen 32 of the delivery catheter 12. However, as shown in Figure 8b, when fluid or some substances injected in the distal direction through the lumen 32 of the catheter 12, the pressure of the fluid or other substance will overcome the bias of the spring 40, causing the tip member 42 to advance to a second position whereby the side opening of the fluid flow channel 44 becomes 30 unobstructed and the injected substance or fluid is permitted to flow outwardly through the fluid flow channel 44 and out of its side opening, into the surrounding tissue. Thereafter, when the substance or fluid is no longer being injected, the bias

of the spring 40 will cause the tip member 42 to retract to its first position as shown in Figure 8a.

In the embodiment shown in Figures 9a and 9b, there is provided a delivery catheter 12 that has an open distal end, a generally conical tip member 408 and a coil spring member 46 which attaches the tip member 408 to the distal end of the catheter 12. The coil spring member 46 is biased to a retracted position, as shown in Figure 9a, wherein the convolutions of the coil spring member 46 are drawn into abutment with one another and with the respective ends of the catheter body 12 and tip member 408. In this manner the distal end of the catheter 12 is substantially closed, and cellular ingrowth or other matter is prevented from invading the lumen of the catheter 12. However, as shown in Figure 9b, when a fluid or substance is injected through the lumen of the catheter 12 the pressure of the injected fluid or substance will overcome the bias of the coil spring member 46, thereby causing the tip member 408 to advance in the distal direction and the convolutions of the coil spring member 46 to separate such that spaces 46a will exist between the individual convolutions of the coil spring member 46. The injected substance or fluid will thus flow outwardly through the spaces 46a and into the surrounding tissue. After the injection of the substance or fluid has stopped, the bias of the coil spring member 46 will cause the tip member 408 to become retracted and the device will assume its closed configuration as shown in Figure 9a.

Another way in which the patency of the lumen of the delivery catheter 12 may be maintained is by constant infusion and withdrawal of fluid therethrough. In this regard, fluid may be continually or periodically infused into a tissue pocket or reservoir at the distal end of the delivery catheter 12 and subsequently re-aspirated through the delivery catheter lumen. Alternatively, the delivery catheter 12 may have multiple lumens, one for infusion of fluid and one for withdrawal of fluid, and a periodic or continual infusion and withdrawal of fluid may be performed to keep these lumens of the delivery catheter 12 open and unobstructed with cellular ingrowth, clots, debris or other matter.

30 Apparatus/Substances for Anchoring of Delivery Catheter

The delivery catheter 12 may incorporate mechanical hooks, screws, barbs or other anchoring members (not shown) that engage surrounding tissue and deter

inadvertent migration or movement of the delivery catheter 12 after it has been implanted. Such anchoring members may be formed of bioabsorbable material and may be designed to break away, detach upon delivery of a pulse of energy or to be otherwise jettisoned when the delivery catheter 12 is purposefully removed from the body. In instances where the optional interactive member 52 comprises an energy emitter or electrode, such as a radiofrequency electrode, such interactive member 52 may be actuated after the delivery catheter 12 is in place for the purpose of fusing the catheter 12 to the surrounding tissue. Also, chemical glues, adhesives, or an ingrowth matrix such as a fabric (e.g., a woven material such as Dacron) into which surrounding tissue will grow, may be disposed on the delivery catheter 12 or introduced through the delivery catheter 12 after it is positioned, to deter inadvertent movement of the delivery catheter 12.

Other Surface Treatments of the Delivery Catheter

Apart from the above-described disposition of glues, adhesives or an ingrowth matrix on the surface of the delivery catheter 12 to facilitate its anchoring, there may additionally be other types of surface materials or surface treatments applied to the delivery catheter 12 for various other reasons. For example, the outer surface of at least the portion of the delivery catheter that becomes inserted into the patient's body may be coated or impregnated with an antibiotic or antimicrobial substance (e.g. provodine iodine, silver compounds, etc.) or other drugs or substances that affect the surrounding tissue in a desired way (e.g., a heparin coating that will reduce clot formation in areas adjacent to the catheter or ~~within-the-blood-vessels-through-which-the-catheter-extends~~). One example of an anti-microbial coating that may be applied to the delivery catheter 12 is a proprietary material containing silver, carbon and platinum and used commercially under the name OligonTM (Edwards Lifesciences Corporation, Irvine, California). Examples of commercially available heparin coatings that may be used include heparin-benzalkonium chloride complex, heparin-TDMAC complex and other medical coatings available from STS Biopolymers, Inc. 336 Summit Point Dr., Henrietta, NY.

Apparatus for Creating Pocket into Which Substance or Apparatus is Introduced:

The delivery catheter 12 may optionally incorporate, or may be used in conjunction with, apparatus for creating a pocket (e.g., a void) within tissue located adjacent to the outflow aperture(s) 24 of the delivery catheter 12 such that substances infused through or apparatus introduced through the delivery catheter 12 will be received within that pocket. For example, an expandable cage may be deployable through or from the delivery catheter 12 to spread or separate the adjacent tissue, thereby creating the desired pocket. Or, the above-described interactive member 52 may comprise an energy emitting apparatus capable of creating a pocket adjacent thereto. In this regard, the interactive member 52 may comprise a radiofrequency electrode that, when actuated, will ablate the adjacent tissue thereby creating the desired pocket. Alternatively, the pocket creating apparatus may comprise a laser port through which ablative laser energy may pass into the adjacent tissue, or a nozzle through which a high pressure jet of fluid may be injected so as to sever or separate the adjacent tissue, thereby creating the pocket.

Variable Delivery Catheter Trajectory from Single Penetrator

Figure 13 shows that the vessel wall penetrator 85 may be of a pre-bent, curved configuration such that incremental advancement of the penetrator may cause its distal tip to be incrementally positioned at a series of different locates, such as point A (PA), point B (PB), point C (PC) and point D (PD) shown in Figure 13. The delivery catheter 12 may then be advanced out of the penetrator at each of the points and drug or substances may be injected at periodic depot locations DL along the path of each advancement or retraction of the delivery catheter 12. In this manner, the drug or other substance may be deposited relatively uniformly over a generally wedge shaped region of tissue with only one penetration through the vessel wall.

B. Procedure for Transluminal Placement of a Delivery Catheter Within and Interstitial Target Site and Acute or Chronic Delivery of Substances or Apparatus to The Target Site:

Figure 1 generally depicts a catheter system 10 of the above-described type being used to perform a procedure for transvenous placement of a delivery catheter 12 in an ischemic region of the patient's myocardium (i.e., the target site) so that a substance or apparatus may be acutely or chronically delivered directly into the 5 target site.

This procedure begins with the percutaneous insertion of the vessel wall 10 penetrating catheter 11 into the patient's femoral vein and advancement of the vessel wall penetrating catheter 11 through the inferior vena cava, through the right atrium, through the coronary venous sinus and into a coronary vein as shown in detail in Figure 11. A vessel wall penetrator 85 is then advanced from the vessel 15 wall penetrating catheter 11 and through the wall of the coronary vein in which the vessel wall penetrating catheter 11 is positioned. Thereafter, a delivery catheter 12 is advanced through the vessel wall penetrator 85 to the target location within the patient's myocardium.

15 In many applications, the vessel wall penetrating catheter 11 will be provided with or associated with guidance elements as described hereabove to guide the positioning, rotational orientation of the catheter 11 within the patient's body and/or the path, trajectory and extent of advancement of the penetrator 85. Typically, these guidance elements will be used to guide the longitudinal position and 20 rotational orientation of the vessel wall penetrating catheter 11 before the penetrator 85 is advanced from the catheter 11. Thereafter, after the delivery catheter 12 has been advanced through the penetrator 85 to the target site, the —penetrator-85-may-be-retracted-into-the-vessel-wall-penetrating-catheter-11-and the vessel wall penetrating catheter 11 may be withdrawn and removed, leaving only 25 the delivery catheter 12 in place.

30 Optionally, as shown in Figure 2c, an interactive member 52 such as an emitter, sensor, marker, electrode, etc. may be mounted on the delivery catheter 12. This interactive member 52 may be sensor (e.g., an electrode, optical sensor, chemical sensor, strain gage, flow meter, etc) that is connected to a receiver or instrumentation located outside the patient's body so as to provide information or analytical data regarding from the target site TS. Examples of the types of information or data that may be sensed and provided from the target site include

ECG, contractility, force of contraction, pressure, local ECG amplitude, local protein levels, local antibody levels, pO_2 , pCO_2 , oxygen saturation, blood flow rate, pH, local lactate levels, etc.

Substances or apparatus may be introduced through the lumen of the delivery catheter 12 at desired time points or intervals. Also, separate sensor(s) or other separate apparatus may be delivered through the delivery catheter 12 so as to provide diagnostic information or other information regarding the physiological status of the myocardium in which the delivery catheter 12 is indwelling and/or the specific positioning of the distal end of the second catheter 12. After all of the desired sampling, diagnosis, delivery of substances and/or delivery of apparatus has been completed, the dosing catheter 12 may then be removed from the body of the patient. Some examples of tissue penetrating catheters 10 useable in this invention include those described in PCT International Patent Publications No. PCT/US99/07115 and PCT/US99/07112.

The delivery catheter 12 may comprise any suitable type of flexible catheter sized to pass through the lumen of the vessel wall penetrator 85 in the manner described here above. Examples of commercially available extrusion that may be used to form the delivery catheter 12 include a

When the invention is used to deliver substances (e.g., drugs, therapeutic agents, biologicals, etc.) to ischemic site(s) within the myocardium, the types of substances that may be delivered include angiogenic factors (e.g. VEGF, FGF, EGF, PDGF or Hepatocyte Growth Factor ("HGF")), gene therapy compositions (e.g. a replication-deficient adenovirus vector containing a transgene which codes for an angiogenic protein or peptide), pro-angiogenic agents or combinations (e.g. an adenosine receptor agonist in combination with heparin), myocardial cells, myocytes, myoblasts, or other cardiac or systemic drugs such as antiarrhythmic agents, beta blockers, calcium channel antagonists, platelet glycoprotein (GP) IIb/IIIa inhibitors, etc.

In some applications, the invention may be used to treat neurodegenerative diseases such as Parkinson's Disease, Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease), Alzheimer's Disease, etc.) By delivering to a target site within the brain or central nervous system a substance that delays the nerve cell degeneration or

causes new nerve cells or new nerve cell connections to form, such substances including but not limited to glial cell line-derived neurotropic factor (GDNF), nerve growth factor, neuro-immunophilin ligand, poly ADP-Ribose polymerase, and combinations thereof.

5 In some applications of the invention, the delivery catheter 12 will be provided with small side apertures 24 and a closed distal end, or some other aperture or nozzle arrangement, that causes the substance to be expelled from the delivery catheter 12 in fine, high velocity jets or streams such that dissemination of the substance into the surrounding tissue will be enhanced. In some instances an
10 10 interactive member 52 on the delivery catheter may be used emit energy or otherwise interact with the delivered substance to affect the substance in a desired way (e.g., to emit an iontophoretic field to drive the substance into adjacent tissue or to cause the distal tip of the delivery catheter 11 to become warm or to vibrate ultrasonically in a way that enhances the distribution or cell membrane permeation
15 15 of the substance). Also, in some applications, a substance injected through the delivery catheter 12 may be mixed with or followed by a second substance which causes the first substance to solidify, gel, adhere or to become otherwise altered in a desired manner (e.g., in a way that affects the distribution, bioavailability, potency, duration of action or pharmacologic activity of the first substance. In this
20 20 regard, a mixture of angiogenic factors (e.g., VegF and FGF) may be prepared in a liquid polymer matrix and injected in a bolus through the delivery catheter 12 into a myocardial target site. Thereafter, a second solution containing a catalyst that causes the polymer matrix to solidify to form a biodegradable solid may be injected as a second bolus through the delivery catheter. The mixture of the fist solution
25 25 with the second solution within the target site will cause the fist solution to solidify in the form of a biodegradable solid or foam. This in situ solidification of the matrix will cause the injected angiogenic factors to remain within the target site for a longer period of time than if they had been injected and allowed to remain as an aqueous solution. Examples of materials that may be formed in situ in this application
30 30 include those described in United States Patent No. 6,139,574 (Vacanti).

The present invention allows for mapping or assessment of the site at which the delivery catheter 12 is positioned to confirm that the site is, or continues to be,

suitable for the intended purpose. For example, a radio-labeled compound, radio-isotope or other traceable substance may be introduced through the delivery catheter and the rate at which the radio-labeled substance or isotope distributes away from the injection site may be measured by well known techniques. If the 5 distribution away from the site is determined to be too rapid or too slow, the delivery catheter 12 may be repositioned before the desired therapeutic or diagnostic substance is injected. In chronic dosing applications wherein the delivery catheter 12 remains indwelling for days or months, this technique may be used to ensure that the delivery catheter 12 has not migrated or moved from the intended injection 10 site, or that the site has not become excessively vascularized since delivery of the last dose. In some applications, it may be desirable for the delivery catheter 12 to have multiple lumens, such that the desired therapeutic or diagnostic substance or apparatus may be delivered through one lumen and a traceable substance useable for mapping or assessment of the target site may be delivered through another 15 lumen.

It will be appreciated that the above-described examples of the application of the catheter system 10 may further be combined with some or all of the other optional elements of the catheter system 10 described here above, such as the high-pressure distribution nozzles, tissue-pocket-creating apparatus, sponges or 20 other apparatus/substances afford to wait or affect the dissemination or distribution of the injected substance, anti-obstruction apparatus, apparatus/substances for a three of the delivery catheter, sensors or other apparatus for characterization of the targets.i.e..or regions adjacent the delivery catheter,-etc.

C. Method for Intravenous Retroperfusion

25 The present invention further includes a method wherein a retrovenous delivery catheter 112, a shown in Figures 11 and 12, is used to deliver a substance into a vein while temporarily obstructing the vein, thereby allowing the substance to enter a target site by undergoing retrograde flow through the venous vasculature to a capillary bed at the target site. The retrovenous delivery catheter 112 30 generally comprises a flexible tubular catheter described hereabove of the above-described type may be inserted into a selected vein (e.g., a coronary vein) and used acutely or chronically to deliver substances to a particular target site by

retroperfusion of the substance through the vein, to a capillary bed located within the target site. An example of this embodiment of the invention is shown in Figures 11 and 12. As shown, the retrovenous catheter 112 has a distal end opening and an inflatable occlusion balloon 50 formed a spaced distance proximal to the distal 5 end opening. The catheter 112 is inserted into the venous vasculature and advanced into a specific vein such as a coronary vein located near an area of ischemic myocardium, as shown in Figures 11 and 12. Before a desired substance is delivered through the catheter 112, the occlusion balloon 50 is inflated so as to occlude the vein and prevent venous blood from flowing through the vein in the 10 normal direction of venous blood flow. The desired substance (e.g., a drug or biological) is then injected through the catheter 112 and out of its distal end opening into the vein. Because the vein is occluded by the balloon, the injected substance will flow in retrograde fashion through the vein and to the capillary bed within the ischemic region of the myocardium. The balloon may remain inflated for a desired 15 period of time to allow the drug or substance to be effectively absorbed by the tissues adjacent to that capillary bed. Thereafter, the balloon is deflated, allowing normal venous flow through the vein. The catheter 112 may be removed after a single dose is delivered or it may remain indwelling for a period of time (e.g., hours, days, weeks or months) to permit repeated doses to be delivered by repeating the 20 foregoing injection procedure. Any or all of the attributes and options described above with respect to the extravascular delivery catheter 12 may also be incorporated into this retrovenous delivery catheter 112, to the extent feasible and ~~not adverse to the intended function of this retrovenous delivery catheter~~ as described herein.

25 **D. Catheter Devices For Intramyocardial Delivery of Substances or Articles Via an Endocardial Approach**

Although the following examples relate to applications wherein the penetrating catheter is positioned within a chamber of the heart, it is to be understood that the methods, devices and systems described and claimed in this 30 regard are useable, not only in chambers of the heart, but in any anatomical cavity, lumen or structure that is substantially larger in diameter than the outer diameter of the penetrating catheter used.

Figures 14-19 show embodiments of the invention that may be used for delivery of substances or articles into the myocardial wall via an endocardial approach. In these embodiments, the tissue penetrating catheter 10, 200 or 200a is advanced through the vasculature to a position within a chamber of the heart.

5 Thereafter the penetrator 85, 204 or 206 is advanced from the catheter body 13, 202 or 202a and into the adjacent wall of the heart. A delivery catheter 12 is then advanced through the lumen of the penetrator 85, 204 or 206 and into the myocardium. A desired substance may then be injected through the delivery catheter 12 and onto the myocardium at desired location(s). As explained 10 herebelow, the configuration of the penetrator 85, 204, 206 may control the direction in which the delivery catheter 12 advances. In particular, the penetrator 85, 204 or 206 may be configured such that it directs the delivery catheter 12 in a direction that is substantially or roughly parallel to the adjacent endocardial wall of the myocardium.

15 Referring specifically to Figures 14 and 15, there is shown a catheter system 200 comprising an elongate flexible catheter body 202 having a distal end opening 203 out of which a resilient tissue penetrator 204 is advanceable. The tissue penetrator 204 in the particular embodiment shown comprises a hollow needle. The penetrator 204 that is pre-bent such that a single, gradual 90° bend is formed 20 therein, as shown. In operation, the catheter body 202 is advanced through the vasculature and into a chamber of the heart (e.g., the left ventricle). With the penetrator 204 retracted within the catheter body 202, the distal end DE of the catheter body 202 is placed in abutting contact with, or close to, the endocardial surface of the myocardium. Thereafter, the penetrator 204 is advanced out of the 25 distal end opening 203 and into the myocardium M. The approximate 90° bend formed in the penetrator 204 causes the distal tip of the fully advanced penetrator 204 to be aimed in a direction that is generally perpendicular to the longitudinal axis of the catheter body 202 and generally parallel to the endocardial surface of the myocardium. The delivery catheter 12 is then advanced through the lumen or 30 bore of the hollow penetrator 204, out of the distal end of the penetrator 204 and through a quantity of myocardial tissue in a direction that is generally parallel to the endocardial surface of the myocardium. The desired drug or substance is then

injected through the delivery catheter 12. As described above in relation to another embodiment, it is possible to create a continuous trail of substance or a plurality of spaced-apart substance deposition sites by slowly withdrawing or advancing the delivery catheter 12 while continuously or periodically injecting the desired 5 substance through the delivery catheter. If subsequent dosing or later delivery of substance or apparatus is desired, the penetrator 204 may be retracted into the catheter body 202 and the penetrating catheter 200 may be removed, leaving the delivery catheter 12 in place for subsequent use.

With specific reference to Figure 16, there is shown an alternative or 10 modified embodiment of the catheter system 200a wherein the tissue penetrator 206 comprises a resilient hollow needle that is preformed to a helical or corkscrew configuration. As in the embodiment shown in Figures 14-15, the catheter body 202a is advanced into a chamber of the heart and maneuvered to a position where its distal end is in abutment with or close-spaced to the endocardial surface of the 15 myocardium. Thereafter, the penetrator 206 is advanced out of the catheter's distal opening 203a and the penetrator 206 is rotated as it is advanced into the myocardium. The rotation of the penetrator 206 as it is advanced causes the corkscrew penetrator 206 to essentially screw into the myocardium. The delivery catheter 12 is then advanced through the lumen of the penetrator and into the 20 myocardium where it is used, in the manner described above, to deliver the desired substance in a desired deposition area 207 (e.g., a trail, elongate track, series of depots or deposits, in a line, etc.). It will be appreciated that, in this embodiment, ~~after one deposition area 207 has been created, the delivery catheter 12 may be retracted into the lumen of the penetrator 206 and the penetrator 206 may be rotated to a new position, at which time the delivery catheter may once again be advanced into an area of myocardial tissue that is different from the area into which the delivery catheter had been previously advanced. In this manner, an array of substance deposition patterns 207 may be formed in a substantial 360° radius around the central axis of the corkscrew penetrator 206 as illustrated in Figure 16a.~~ 25 30 If subsequent dosing or later delivery of substance or apparatus is desired, the penetrator 206 may be rotatably retracted into the catheter body 202a and the

penetrating catheter 200a may be removed, leaving the delivery catheter 12 in place for subsequent use.

Figure 17 shows an example of the use of a side exiting penetrating catheter system 10a that is a modification of that type shown in Figures 2 and 2a. This 5 catheter system is also useable to accomplish the delivery of a substance into the myocardial wall, via an endocardial approach. In the example shown in Figure 17, the tissue penetrating catheter 10a comprises a catheter body 13a which may be the same or similar to that shown in Figures 2 and 2a or may be constructed in any suitable manner known in the art of catheter design and construction. A penetrator 10 exit port 37a is formed in the catheter body 13a and a curved penetrator 85a comprising a hollow needle is advanceable from the exit port 37a as shown in the example of Figure 17. An optional guide catheter may be used to guide the penetrating catheter to a position adjacent the wall of the atrium or ventricle in the area where it is desired to deliver the substance (or article). In operation, the 15 penetrating catheter body 13 is maneuvered into juxtaposition with the endocardial surface of the myocardium, with or without the use of the optional guide catheter 210. The penetrating catheter 10a is then placed in a rotational orientation whereby the side exit port 37a is aimed at or directly juxtaposed with the endocardial surface to be penetrated. Optional rotational-orientation-indicating 20 markers on the catheter body 13a, imaging apparatus (on board the catheter body 13a or located elsewhere), electro-anatomical catheter navigation systems or other apparatus for discerning the specific rotational orientation of the catheter relative to the trajectory-or-path-upon-which-the penetrator-85a-will-advance, may be used as described above and in the prior patent applications incorporated herein by 25 reference. After the exit port 37a has been positioned in juxtaposition to the endocardial surface, the penetrator 85a is advanced into the adjacent myocardial tissue. The curve(s) and shape of the penetrator 85a are such that as it advances it reaches a position where its distal tip is directed generally parallel to the endocardial surface, as shown in Figure 17. Thereafter, the delivery catheter 12 is advanced through the penetrator 85a and into the myocardium. As in the other 30 embodiments described above, the positioning and shape of the penetrator causes the delivery catheter to advance on a path that does not result in the delivery

catheter a) repuncturing through the endocardium and into the chamber of the heart or b) passing outwardly through the epicardial surface of the heart and/or c) perforating a substantially sized coronary blood vessel in a manner that would cause untoward bleeding or other potential complications. The substance (or 5 article) is then injected through the delivery catheter and into the myocardium. As described above in relation to the other embodiments, it is possible to create multiple spaced-apart intramyocardial depots of a substance or a continuous, elongate depot of the substance by slowly advancing or retracting the delivery catheter 85a while continuously or periodically injecting the desired substance. If 10 subsequent dosing or later delivery of substance or apparatus is desired, the penetrator 85a may be retracted into the catheter body 13a and the penetrating catheter 10 may be removed, leaving the delivery catheter 12 in place for subsequent use.

Figures 18 and 19 show an example of a procedure wherein a therapeutic substance (e.g., myoblasts, angiogenic factors, muscle grafts, etc.) may be deposited directly into an infarct zone IZ wherein myocardial tissue has become necrotic. In this example, the penetrating catheter 10 has been advanced into a coronary vein CV adjacent to the infarct zone IZ. A penetrator 85 having an approximate 90 degree curvature is advanced from the penetrating catheter 10, 20 though the wall of the coronary vein CV and into or near the infarct zone IZ. The delivery catheter 12 is then advanced through the lumen of the penetrator 85 and through all or a portion of the infarct zone, as specifically shown in Figure 19. Thereafter, as the therapeutic substance is being injected through the delivery catheter 12, the delivery catheter 12 is slowly retracted in the proximal direction 25 (see arrows on Figure 19), thereby providing an elongate deposition pattern DP wherein the therapeutic substance is deposited. In addition to the area where the delivery catheter 12 is being used to deposit the therapeutic substance, Figure 19 also illustrates a previously created deposition pattern DP (see cross-hatched area on Figure 19). This previously created deposition pattern DP is an elongate region, 30 as shown. A deposition pattern axis DPA projected through the elongate deposition pattern DP is non-perpendicular and preferable tangential or nearly tangential to the adjacent endocardial surfaces of the right and left ventricles RV, LV. As explained

hereabove, this generally tangential or non-perpendicular approach allows a greater length of delivery catheter 12 to be advanced into the myocardium than would have been possible if the penetrator 85 had been aimed or directed such that the delivery catheter 12 advanced perpendicular to and toward the left or right ventricle LV, RV.

5

The procedure illustrated in Figures 18-19 may be used to revitalize or restore function to regions of the myocardium that are necrotic or severely damaged. Thus, this technique may be useable to treat congestive heart failure. In addition to the deposition of myoblasts, stem cells, other cellular preparations, 10 angiogenic factors, drugs or other therapeutic substances intended to improve the contractility or function of the impaired myocardium, this technique may also be used to implant grafts of muscle tissue into the myocardium. In this regard, a coring needle may be used to harvest an elongate segment of healthy cardiac or other muscle tissue. That harvested tissue graft may then be loaded into the 15 delivery catheter 12 and deposited into the infarct zone IZ as the delivery catheter 12 is retracted, thereby creating an elongate tissue graft that extends fully or partially through the infarct zone IZ.

Although exemplary embodiments of the invention have been shown and described, many changes, modifications and substitutions may be made by those 20 having ordinary skill in the art without necessarily departing from the spirit and scope of this invention. Specifically, elements or attributes described in connection with one embodiment may also be used in connection with another embodiment provided that the inclusion or use of such element or attribute would not render the embodiment in which it is incorporated unuseable or otherwise undesirable for an 25 intended application. Accordingly, all such additions, deletions, modifications and variations to the above-described embodiments are to be included within the scope of the following claims.

CLAIMS

What is claimed is:

1. 1. A system for delivering substances or apparatus to an extravascular target site within the body of a human or veterinary patient, said system comprising:
 4. a. a vessel wall penetrating catheter that comprises i) a catheter body that is insertable into the vasculature of the patient and ii) a vessel wall penetrating member having a lumen extending longitudinally therethrough, said penetrating member being passable from the catheter body and through the wall of a blood vessel in which the catheter body is positioned; and,
 - 10
 11. b. a delivery catheter having a lumen extending longitudinally therethrough, said delivery catheter being advanceable through the lumen of the vessel wall penetrating member to an extravascular target site;
 - 15
 16. said vessel wall penetrating member being retractable into the catheter body of the vessel wall penetrating catheter and the vessel wall penetrating catheter being removable from the patient's body such that the delivery catheter remains -indwelling-with-the-distal-end-of-the-delivery-catheter-located-at-the-extravascular target site.
1. 2. A system according to Claim 1 wherein the vessel wall penetrating catheter further comprises iii) a guidance element useable by the operator to position the vessel wall penetrating catheter body within the vasculature of the patient such that when the vessel wall penetrating member is passed from the catheter body it will penetrate through the wall of the blood vessel in the direction of the intended extravascular target site.

- 1 3. A system according to Claim 2 wherein the guidance element comprises an
2 imaging apparatus.
- 1 4. A system according to Claim 3 wherein the imaging apparatus is an
2 ultrasound imaging apparatus.
- 1 5. A system according to Claim 2 wherein the guidance element comprises an
2 imageable marker on the vessel wall penetrating catheter body.
- 1 6. A system according to Claim 2 wherein the guidance element comprises the
2 combination of an imaging apparatus and at least one imageable marker that is
3 imageable by the imaging apparatus.
- 1 7. A system according to Claim 2 wherein the guidance element comprises an
2 emitter located on or in the catheter body, said emitter emitting a signal that is
3 received by an extracorporeally situated signal-receiving apparatus.
- 1 8. A system according to Claim 1 wherein the delivery catheter further
2 comprises a matter blocking member for preventing cellular ingrowth and other
3 matter from obstructing the lumen of the delivery catheter.
- 1 9. A system according to Claim 8 wherein the delivery catheter has an outflow
2 opening through which substances may pass out of the lumen of the delivery
3 catheter and into the target location and wherein the matter blocking member
4 comprises a selectively permeable barrier that allows desired substances to be
5 infused in the distal direction through the outflow opening and to the target location
6 but prevents cellular ingrowth and other matter from entering the lumen of the
7 delivery catheter through said outflow opening.
- 1 10. A system according to Claim 9 wherein the selectively permeable barrier is
2 a balloon attached to the delivery catheter such that substances infused through

1 the lumen of the delivery catheter collect within the balloon and subsequently
2 diffuse outwardly through the balloon.

1 11. A system according to Claim 8 wherein the matter blocking member
2 comprises a stylet that is insertable into the lumen of the delivery catheter to block
3 the entry of extraneous matter thereinto.

1 12. A system according to Claim 11 wherein the stylet is removable from the
2 lumen of the delivery catheter to permit delivery of a substance or apparatus
3 through the delivery catheter.

1 13. A system according to Claim 1 wherein the delivery catheter comprises:
2 a first tube having a lumen and a sidewall in which an outflow aperture is
3 formed; and,
4 a second tube rotatably disposed in a coaxial position within the first tube,
5 said second tube having a lumen, a closed distal end and a sidewall in which an
6 opening is formed;
7 the second tube being rotatably moveable between i) a blocking position
8 wherein the side wall of the second tube substantially blocks the outflow aperture
9 of the first tube to prevent cellular ingrowth and other matter from entering the
10 lumen of the second tube and ii) an infusion position wherein the opening of the
11 second tube is aligned with the outflow opening of the first tube such that a
12 substance—that—is—jected—into—the—lumen—of—the—second—tube—will—flow—through—the
13 opening of the second tube and through the outflow opening of the first tube.

1 14. A system according to Claim 12 wherein a plurality of outflow apertures are
2 formed in the sidewall of the first tube.

1 15. A system according to Claim 1 wherein the delivery catheter comprises:
2 a tube having a lumen and a sidewall in which an outflow aperture is formed;
3 and,

4 an obturator member disposed at least partially within the lumen of the tube,
5 said obturator member being alternately disposable in i) a blocking position wherein
6 the obturator substantially blocks the outflow aperture of the tube to prevent cellular
7 ingrowth and other matter from entering the lumen of the tube and ii) an infusion
8 position wherein the obturator does not substantially block the outflow apertures
9 such that fluid may be injected through the lumen of the tube and out of the outflow
10 aperture.

1 16. A system according to Claim 15 wherein a plurality of outflow apertures are
2 formed in the sidewall of the tube.

1 17. A system according to Claim 15 wherein the obturator member is an
2 inflatable balloon that assumes said blocking position when inflated and said
3 infusion position when deflated.

1 18. A system according to Claim 1 wherein the delivery catheter comprises an
2 infusion lumen, a return lumen, an outflow aperture through which infused
3 substances may flow out of the infusion lumen and a flow diverter, said flow diverter
4 that is alternately deployable in i) an infusion position whereby substances infused
5 through the infusion lumen will flow out of the outflow aperture and ii) a recirculation
6 position whereby fluid infused through the infusion lumen will be recirculated back
7 through the return lumen.

1 19. A system according to Claim 1 wherein the delivery catheter comprises a
2 pressure increasing outflow opening configured to cause an increase the pressure
3 of fluids that are injected through the delivery catheter lumen and out of said
4 pressure increasing outflow opening.

1 20. A system according to Claim 19 wherein said pressure increasing outflow
2 opening is formed in the side wall of the delivery catheter.

- 1 21. A system according to Claim 20 wherein a plurality of pressure increasing
- 2 outflow openings are formed in the side wall of the delivery catheter.
- 1 22. A system according to Claim 1 wherein the delivery catheter further
- 2 comprises an anchoring member for anchoring the catheter in a substantially fixed
- 3 position within the patient's body.
- 1 23. A system according to Claim 22 wherein the anchoring member is selected
- 2 from the group of anchoring members consisting of:
 - 3 a hook;
 - 4 a barb;
 - 5 a permeable surface into which tissue may grow;
 - 6 an adhesive; and,
 - 7 combinations thereof.
- 1 24. A system according to Claim 1 wherein the delivery catheter further
- 2 comprises a backflow deterrent member for blocking backflow of substances that
- 3 have been injected through the delivery catheter.
- 1 25. A system according to Claim 24 wherein said backflow deterrent member
- 2 comprises a backflow barrier rib formed on the delivery catheter.
- 1 26. A system according to Claim 25 wherein said backflow barrier comprises an
- 2 inflatable balloon on the delivery catheter.
- 1 27. A system according to Claim 25 wherein said backflow barrier comprises a
- 2 raised projection formed on the exterior of the delivery catheter.
- 1 28. A system according to Claim 27 wherein the raised projection comprises an
- 2 annular rib formed about the outer surface of the delivery catheter

- 1 29. A system according to Claim 24 wherein the backflow deterrent comprises
- 2 a sealant that is implanted prior to or concurrently with removal of the delivery
- 3 catheter so as to prevent the injected substance from bacflowing through the tract
- 4 from which the delivery catheter is removed.
- 1 30. A system according to Claim 29 wherein the sealant comprises a quantity
- 2 of a flowable sealant injected into the tract upon removal of the delivery catheter.
- 1 31. A system according to Claim 29 wherein the sealant comprises a detachable
- 2 sealing member.
- 1 32. A system according to Claim 31 wherein the detachable sealing member is
- 2 formed of biodegradable material.
- 1 33. A system according to Claim 32 wherein the sealing member is a collagen
- 2 sponge.
- 1 34. A system according to Claim 32 wherein the sealing member is a hydrogel
- 2 sponge.
- 1 35. A system according to Claim 1 wherein at least a portion of the delivery
- 2 catheter is coated with an adhesive.
- 1 36. A system according to Claim 1 wherein an anti-microbial substance is
- 2 disposed on at least a portion of the delivery catheter.
- 1 37. A system according to Claim 1 wherein an anti-coagulant substance is
- 2 disposed on at least a portion of the delivery catheter.
- 1 38. A system according to Claim 1 further comprising apparatus for creating a
- 2 pocket within tissue adjacent to the delivery catheter such that when a substance

1 or apparatus is introduced through the delivery catheter it will be received within
2 said pocket.

1 39. A system according to Claim 38 wherein the apparatus for creating a pocket
2 comprises an energy emitting member that emits energy into adjacent tissue to
3 create said pocket.

1 40. A system according to Claim 39 wherein the energy emitting apparatus is a
2 radiofrequency electrode.

1 41. A system according to Claim 39 wherein the energy emitting apparatus is a
2 laser.

1 42. A system according to Claim 38 wherein the apparatus for creating a pocket
2 comprises a nozzle through which a stream of fluid may be injected to create the
3 pocket in adjacent tissue.

1 43. A system according to Claim 38 wherein the apparatus for creating a pocket
2 comprises an expandable cage which, when expanded, creates said pocket.

3
4 44. A system according to Claim 1 further in combination with an infusion
5 apparatus for infusing a substance through the delivery catheter.

1 45. A system according to Claim 44 wherein said infusion apparatus is a syringe.

1 46. A system according to Claim 44 wherein said infusion apparatus is a pump.

1 47. A system according to Claim 44 wherein said infusion apparatus is a
2 reservoir positioned for gravity drainage of the substance through the delivery
3 catheter.

- 1 48. A system according to Claim 44 wherein said infusion apparatus further
- 2 comprises a quantity of a substance for infusion through the delivery catheter.
- 1 49. A system according to Claim 48 wherein the substance is a drug.
- 1 50. A system according to Claim 49 wherein the drug is selected from the group
- 2 consisting of: thrombolytics, platelet inhibitors, anti-restenotic agents, beta
- 3 adrenergic blockers, ion channel antagonists, positive or negative ionotropic
- 4 agents, anti-arrhythmics and combinations thereof.
- 1 51. A system according to Claim 48 wherein the substance is a protein.
- 1 52. A system according to Claim 48 wherein the substance is an angiogenic
- 2 substance.
- 1 53. A system according to Claim 51 wherein the angiogenic substance is
- 2 selected from the group consisting of vascular endothelial growth factor (VEGF),
- 3 fibroblast growth factors (FGF), epidermal growth factor (EGF), platelet-derived
- 4 growth factor (PDGF), hepatocyte growth factor (HGF) or scatter factor, heparin
- 5 combined with an adenosine receptor agonist, and combinations thereof.
- 1 54. A system according to Claim 48 wherein the substance comprises cells.
- 1 55. A system according to Claim 54 wherein the substance comprises
- 2 progenitor cells for a type of cell that is desired to be formed at the target site.
- 1 56. A system according to Claim 55 wherein said substance comprises
- 2 myoblasts to form cardiac muscle cells.
- 1 57. A system according to Claim 56 wherein said cells are selected from the
- 2 group consisting of stem cells, progenitor cells, myoblasts, myocytes, secretory
- 3 cells, pancreatic islet cells, dopamine secreting cells, endothelial cells, hepatocytes,

1 cloned cells, cells grown in cell culture, genetically modified cells, and combinations
2 thereof.

1 58. A system according to Claim 48 wherein the substance is a gene.

1 59. A system according to Claim 48 wherein the substance comprises a gene
2 and a vector for facilitating entry of the gene into locations within cells at which the
3 gene will have a desired effect on the cells.

1 60. A system according to Claim 59 wherein the vector is a virus.

1 61. A method for delivering a substance or apparatus to an extravascular target
2 site within the body of a human or veterinary patient, said method comprising the
3 steps of:

4

5 (A) providing a vessel wall penetrating catheter that is insertable into the
6 vasculature of the patient, said vessel wall penetrating catheter
7 having a penetrating member that is advanceable through the wall of
8 a blood vessel in which the catheter body is positioned, said vessel
9 wall penetrating member having a lumen extending longitudinally
10 therethrough;

11

12 (B) inserting the vessel wall penetrating catheter into the vasculature of
13 the patient;

14

15 (C) positioning the vessel wall penetrating catheter within the vasculature
16 of the patient such that the penetrator, when advanced, will pass
17 through the wall of a blood vessel to a location near the target site;

18

19 (D) advancing the penetrator through the wall of a blood vessel and to
20 a location near the target site;

21

22 (E) advancing through the lumen of the penetrator and to the target site,
23 a second apparatus selected from the group consisting of:
24 i. an elongate delivery catheter having a lumen through
25 which a substance may be injected or withdrawn;
26 ii. an elongate member that comprises a therapeutic
27 apparatus operative to deliver a therapy to the target
28 site;
29 iii. an elongate member that comprises an information-
30 obtaining apparatus operative to obtain information
31 from the target site; and,
32 iv. possible combinations thereof.

1 62. A method according to Claim 61 wherein the vessel wall penetrating catheter
2 further comprises a guidance element useable by the operator to position the
3 vessel wall penetrating catheter body within the vasculature of the patient such that
4 when the vessel wall penetrating member is passed from the catheter body it will
5 penetrate through the wall of the blood vessel in the direction of the intended
6 extravascular target site, and wherein Step C further comprises using said guidance
7 element to position the vessel wall penetrating catheter body within the vasculature
8 of the patient such that when the vessel wall penetrating member is passed from
9 the catheter body it will penetrate through the wall of the blood vessel in the
10 direction of the intended extravascular target site.

1 63. A method according to Claim 62 wherein the guidance element comprises
2 an imaging apparatus and wherein Step C further comprises using the imaging
3 apparatus to image at least the target site and using such image to guide the
4 positioning of the vessel wall penetrating catheter.

1 64. A method according to Claim 63 wherein the imaging apparatus is an
2 ultrasound imaging apparatus and the image used in Step C is an ultrasound
3 image.

1 65. A method according to Claim 62 wherein the guidance element comprises
2 indicia that indicates the path that will be followed by the penetrator when it is
3 subsequently advanced from the catheter penetrating catheter and wherein Step
4 C further comprises obtaining an image of the imageable marker and using such
5 image to guide the positioning of the vessel wall penetrating catheter.

1 66. A method according to Claim 65 wherein the guidance element comprises
2 the combination of an imaging apparatus and at least one imageable marker on the
3 vessel wall penetrating catheter, and wherein Step C further comprises using the
4 imaging apparatus to obtain an image of at least the imageable marker and using
5 that image to guide the positioning of the vessel wall penetrating catheter.

1 67. A method according to Claim 66 wherein the imageable marker provides an
2 indication of the direction in which the penetrator will advance and wherein Step C
3 further comprises imaging of the imageable marker to obtain an indication of the
4 direction in which the penetrator will advance and using said indication to
5 rotationally orient and position the vessel wall penetrating catheter such that
6 subsequent advancement of the penetrator will cause the penetrator to travel in the
7 direction of the target site.

1 68. A method according to Claim 62 wherein the guidance element comprises
2 an emitter located on or in the catheter body, said emitter emitting a signal that is
3 received by an extracorporeally situated signal-receiving apparatus and wherein
4 Step C further comprises using an extracorporeally situated signal-receiving
5 apparatus to receive a signal from the emitter and to thereby guide the placement
6 of the vessel wall penetrating catheter.

1 69. A method according to Claim 61 wherein the second apparatus comprises
2 an elongate delivery catheter having a lumen through which a substance may be
3 delivered and wherein the method further comprises the step of:
4 (F) delivering a substance through the delivery catheter to the target site.

1 70. A method according to Claim 69 wherein the delivery catheter is a delivery
2 catheter having an outer diameter of less than 0.5 mm.

1 71. A method according to Claim 69 wherein the delivery catheter further
2 comprises a matter blocking member for preventing cellular ingrowth and other
3 matter from obstructing the lumen of the delivery catheter and wherein the method
4 further comprises the step of:

5 using said matter blocking member to prevent cellular ingrowth
6 and other matter from obstructing the lumen of the delivery catheter
7 at least during times when no substance is being infused through the
8 delivery catheter.

1 72. A method according to Claim 71 wherein the delivery catheter has an outflow
2 opening through which substances may pass out of the lumen of the delivery
3 catheter and into the target location and wherein the matter blocking member
4 comprises a selectively permeable barrier that allows desired substances to be
5 infused in the distal direction through the outflow opening and to the target location
6 but prevents cellular ingrowth and other matter from entering the lumen of the
7 delivery catheter through said outflow opening, and wherein the method further
8 comprises the step of:

9 infusing a substance in the distal direction through the delivery
10 catheter and, thereafter, allowing the substance to pass outwardly
11 through the selectively permeable barrier.

1 73. A method according to Claim 71 wherein the selectively permeable barrier
2 comprises a balloon attached to the delivery catheter and wherein the method
3 further comprises the step of:

4 infusing a substance the distal direction through the delivery
5 catheter such that the substance collects within the balloon and
6 subsequently diffuses outwardly through the balloon.

1 74. A method according to Claim 71 wherein the matter blocking member
2 comprises a stylet that is insertable into the lumen of the delivery catheter to block
3 cellular ingrowth and other matter from entering thereinto and wherein the method
4 further comprises the step of:

5 inserting the stylet into the lumen of the delivery catheter at
6 least at times when no substance is being infused through said
7 lumen, thereby blocking the entry of cellular ingrowth and other
8 matter into the delivery catheter lumen.

1 75. A method according to Claim 74 wherein the stylet is removable from the
2 lumen of the delivery catheter to permit delivery of a substance or apparatus
3 through the delivery catheter and wherein the method further comprises the step
4 of:

5 removing the stylet from the delivery catheter lumen when it is
6 desired to deliver a substance or apparatus through the delivery
7 catheter lumen.

1 76. A method according to Claim 69 wherein the delivery catheter comprises:
2 a first tube having a lumen and a sidewall in which an outflow aperture is
3 formed; and,
4 a second tube rotatably disposed in a coaxial position within the first tube,
5 said second tube having a lumen, a closed distal end and a sidewall in which an
6 opening is formed;
7 the second tube being rotatably moveable between i) a blocking position
8 wherein the side wall of the second tube substantially blocks the outflow aperture
9 of the first tube to prevent cellular ingrowth and other matter from entering the
10 lumen of the second tube and ii) a delivery position wherein the opening of the
11 second tube is aligned with the outflow opening of the first tube such that a
12 substance that is injected into the lumen of the second tube will flow through the
13 opening of the second tube and through the outflow opening of the first tube, and
14 wherein said method further comprises the steps of:

15 placing the second tube in the blocking position when no
16 substance or apparatus is being delivered through the delivery
17 catheter; and,

18 placing the second tube in the delivery position when a
19 substance or apparatus is being delivered through the delivery
20 catheter.

1 77. A method according to Claim 71 wherein the delivery catheter comprises:
2 a tube having a lumen and a sidewall in which an outflow aperture is formed;
3 and,

4 an obturator member disposed at least partially within the lumen of the tube,
5 said obturator member being alternately disposable in i) a blocking position wherein
6 the obturator substantially blocks the outflow aperture of the tube to prevent cellular
7 ingrowth and other matter from entering the lumen of the tube and ii) a delivery
8 position wherein the obturator does not substantially block the outflow apertures
9 such that fluid may be injected through the lumen of the tube and out of the outflow
10 aperture; and wherein the method further comprises the steps of:

11 placing the obturator in the blocking position when no
12 substance or apparatus is being delivered through the delivery
13 catheter; and,

14 placing the obturator in the delivery position when a substance
15 or apparatus is being delivered through the delivery catheter.

1 78. A method according to Claim 77 wherein the obturator member is an
2 inflatable balloon that assumes said blocking position when inflated and said
3 infusion position when deflated, and wherein the step of placing the obturator in the
4 blocking position comprises inflating the balloon and the step of placing the
5 obturator in the delivery position comprises deflating the balloon.

1 79. A method according to Claim 69 wherein the delivery catheter comprises a
2 delivery lumen, a return lumen, an aperture through which substances or apparatus
3 delivered through the delivery lumen may pass out of the delivery catheter and a

4 flow diverter, said flow diverter that is alternately deployable in i) a delivery position
5 whereby substances or apparatus may be delivered through the delivery catheter
6 lumen and out of the aperture and ii) a recirculation position whereby fluid infused
7 through the delivery lumen will be recirculated back through the return lumen and
8 wherein the method further comprises the steps of:

9 placing the diverter in the delivery position when it is desired
10 to deliver a substance or apparatus through the delivery lumen and
11 out of the aperture; and,

12 placing the diverter in the recirculation position and infusing a
13 fluid through the delivery lumen and back through the recirculation
14 lumen, when no substance or apparatus is being delivered through
15 the delivery lumen.

1 80. A method according to Claim 69 wherein the delivery catheter comprises a
2 pressure increasing outflow opening configured to cause an increase the pressure
3 of substances that are injected through the delivery catheter lumen and out of said
4 pressure increasing outflow opening, and wherein the method further comprises the
5 step of:

6 delivering a substance through the delivery catheter and out
7 of the outflow opening such that the pressure of the substance
8 increases as it flows out of the outflow opening.

1 81. A method according to Claim 69 wherein the substance delivered in Step F
2 is a therapeutic substance.

1 82. A method according to Claim 69 wherein the substance delivered in Step F
2 is a agent that provides an enhanced image of the target site.

1 83. A method according to Claim 69 wherein the substance delivered in Step F
2 is a traceable substance that may be used to determine the rate at which the
3 substance distributes away from or is otherwise inactivated at the target site or
4 other pharmacokinetic or biodistributive parameters or variables.

- 1 84. A method according to Claim 81 wherein the therapeutic substance is
- 2 selected from the group consisting of : a drug, a protein, cells, an angiogenic
- 3 substance, a myogenic substance, a neurogenic substance, a gene, a gene therapy
- 4 composition, genetic material in combination with a vector for delivering the genetic
- 5 material into locations within cells at which the genetic material will have a desired
- 6 effect on the cells;
- 1 85. A method according to Claim 81 wherein the method is carried out to
- 2 improve perfusion of an ischemic target site and where the therapeutic substance
- 3 delivered in Step F comprises is an angiogenic agent that increases vascularity of
- 4 the ischemic target site.
- 1 86. A method according to Claim 85 wherein the angiogenic agent delivered in
- 2 Step F is selected from the group of angiogenic agents consisting of vascular
- 3 endothelial growth factor (VEGF), fibroblast growth factors (FGF), epidermal growth
- 4 factor (EGF), platelet-derived growth factor (PDGF), hepatocyte growth factor
- 5 (HGF)or scatter factor, heparin combined with an adenosine receptor agonist, nerve
- 6 cell growth factor (NGF), and combinations thereof.
- 1 87. A method according to Claim 81 wherein the therapeutic substance delivered
- 2 in Step F comprises cells.
- 1 88. A method according to Claim 87 wherein said cells are selected from the
- 2 group consisting of stem cells, progenitor cells, myoblasts, myocytes, secretory
- 3 cells, pancreatic islet cells, dopamine secreting cells, endothelial cells, hepatocytes,
- 4 cloned cells, cells grown in cell culture, genetically modified cells, and combinations
- 5 thereof.
- 1 89. A method according to Claim 87 wherein the method is carried out to treat
- 2 a condition characterized by a deficiency of a type of cell within the patient's body
- 3 and wherein the type of cell that is deficient matures in situ from stem cells, and

1 wherein the therapeutic substance delivered in Step F comprises stem cells of a
2 type that mature into the deficient cell type.

1 90. A method according to Claim 89 wherein the method is carried out to treat
2 a condition characterized by a lack of living myocytes in or near the target site and
3 wherein the therapeutic substance delivered in Step F comprises myocytes.

1 91. A method according to Claim 89 wherein the method is carried out to treat
2 parkinsonism, the target site comprises the substantia nigra of the patient's brain
3 and wherein the therapeutic substance delivered in Step F comprises dopamine
4 secreting cells which when implanted will increase dopamine in the substantia
5 nigra.

1 92. A method according to Claim 91 wherein the dopamine secreting cells
2 comprise fetal dopamine secreting cells.

1 93. A method according to Claim 89 wherein the method is carried out to treat
2 diabetes, the target site comprises the patient's pancreas, and wherein the
3 therapeutic substance delivered in Step F comprises insulin secreting cells which,
4 when implanted, will increase insulin production by the patient's pancreas.

1 94. A method according to Claim 93 wherein the insulin secreting cells comprise
2 pancreatic- β -islet-cells.

1 95. A method according to Claim 81 wherein the method is carried out to treat
2 a neurogenerative disorder and wherein the substance delivered comprises nerve
3 cells.

1 96. A method according to Claim 81 wherein the method is carried out to treat
2 a neurogenerative disorder and wherein the substance delivered comprises a
3 substance that facilitates nerve growth.

1 97. A method according to Claim 96 wherein the substance delivered is selected
2 from the group consisting of: glial cell line-derived neurotropic factor (GDNF), nerve
3 growth factor, neuro-immunophilin ligand, poly ADP-Ribose polymerase, and
4 combinations thereof.

1 98. A method according to Claim 81 wherein the therapeutic substance
2 comprises a gene in combination with a vector for facilitating entry of the gene into
3 locations within cells in which the gene will have a desired therapeutic effect.

1 99. A method according to Claim 98 wherein the vector is a virus.

1 100. A method according to Claim 61 wherein the second apparatus further
2 comprises an anchoring member for holding the second apparatus in a
3 substantially fixed position within the patient's body and wherein the method further
4 comprises the step of:

5 (F) causing the anchoring apparatus to hold the second apparatus in a
6 substantially fixed position within the patient's body.

1 101. A method according to Claim 100 wherein the anchoring member is selected
2 from the group of anchoring members consisting of:

3 a hook;
4 a barb;
5 a permeable surface into which tissue may grow;
6 an adhesive; and,
7 combinations thereof;

8 and wherein Step F comprises causing the anchoring apparatus to engage
9 tissue adjacent thereto so as to hold the second apparatus in said substantially
10 fixed position.

1 102. A method according to Claim 61 wherein the second apparatus is a delivery
2 catheter, wherein the delivery catheter further comprises a backflow deterrent for

3 blocking backflow of substances that have been injected through the delivery
4 catheter and wherein the method further comprises the step of:

5 causing the backflow deterrent to deter backflow of a substance that has
6 been infused through the delivery catheter to the target site.

1 103. A method according to Claim 102 wherein the backflow deterrent comprises
2 a backflow barrier rib formed on the delivery catheter and wherein the step of
3 causing the backflow deterrent to deter backflow is carried out by positioning the
4 backflow deterrent rib so that it acts as a barrier to the unwanted backflow.

1 104. A method according to Claim 103 wherein said backflow barrier comprises
2 an inflatable balloon on the delivery catheter and wherein the step causing the
3 backflow deterrent to deter backflow is carried out by inflating the balloon.

1 105. A method according to Claim 102 wherein said backflow deterrent comprises
2 a raised projection formed on the exterior of the delivery catheter and wherein the
3 step of causing the backflow deterrent to deter backflow is carried out by positioning
4 the raised projection so that it acts as a barrier to the unwanted backflow.

1 106. A method according to Claim 105 wherein the raised projection comprises
2 an annular rib formed about the outer surface of the delivery catheter

1 107.—A method according to Claim 102 wherein the backflow deterrent comprises
2 a sealant which, when implanted in the penetration tract through which the delivery
3 catheter was advanced, will prevent the substance from bacflowing through that
4 tract, and wherein Step F of the method comprises implanting the sealant into the
5 penetration tract.

1 108. A method according to Claim 107 wherein the sealant is implanted into the
2 tract prior to removal of the delivery catheter.

- 1 109. A method according to Claim 107 wherein the sealant is implanted into the
- 2 tract prior concurrently with removal of the delivery catheter.
- 1 110. A method according to Claim 107 wherein the sealant comprises a quantity
- 2 of a flowable sealant and wherein the step of implanting the sealant into the
- 3 penetration tract comprises injecting the flowable sealant into the penetration tract.
- 1 111. A method according to Claim 110 wherein the injecting of the flowable
- 2 sealant into the penetration tract comprises injecting the flowable sealant through
- 3 the delivery catheter.
- 1 112. A method according to Claim 107 wherein the sealant comprises a
- 2 detachable sealing member and wherein Step F comprises introducing the sealing
- 3 member into the penetration tract and thereafter detaching the sealing member
- 4 such that it will remain in the penetration tract after the delivery catheter has been
- 5 removed.
- 1 113. A method according to Claim 112 wherein the detachable sealing member
- 2 comprises biodegradable material and wherein Step F comprises introducing the
- 3 biodegradable member into the penetration tract and thereafter detaching the
- 4 biodegradable member such that it will remain in the penetration tract after the
- 5 delivery catheter has been removed.

- 1 114. A method according to Claim 112 wherein the sealing member is a collagen
- 2 sponge and wherein Step F comprises introducing the collagen sponge into the
- 3 penetration tract and thereafter detaching the collagen sponge such that it will
- 4 remain in the penetration tract after the delivery catheter has been removed.
- 1 115. A method according to Claim 112 wherein the sealing member is a hydrogel
- 2 material and wherein Step F comprises introducing the hydrogel material into the
- 3 penetration tract and thereafter detaching the hydrogel material such that it will
- 4 remain in the penetration tract after the delivery catheter has been removed.

1 116. A method according to Claim 61 wherein at least a portion of the second
2 apparatus is coated with an adhesive and wherein the method further comprises
3 the step of:

4 (F) causing the adhesive to adhere to adjacent tissue thereby deterring
5 movement of the second apparatus.

1 117. A method according to Claim 61 wherein an anti-microbial substance is
2 disposed on at least a portion of the second apparatus and wherein the method
3 further comprises the step of:

4 (F) causing the anti-microbial substance to deter microbial growth in the
5 area surrounding the portion of the second apparatus on which the
6 anti-microbial substance is disposed.

1 118. A method according to Claim 61 wherein an anti-coagulant substance is
2 disposed on at least a portion of the second apparatus and wherein the method
3 further comprises the step of:

4 (F) causing the anti-coagulant substance to deter coagulative processes
5 in the area surrounding the portion of the second apparatus on which
6 the anti-coagulant substance is disposed.

1 119. A method according to Claim 69 wherein the apparatus further comprises a
2 tissue-pocket-creating-apparatus and wherein the method further comprises the
3 step of:

4 using the tissue pocket creating apparatus to create a pocket within tissue
5 adjacent to the delivery catheter such that when a substance or apparatus is
6 introduced through the delivery catheter it will be received within said pocket

1 120. A method according to Claim 119 wherein the tissue pocket creating
2 apparatus comprises an energy emitting member and wherein the step of using the
3 tissue pocket creating apparatus comprises causing the tissue pocket creating
4 apparatus to emit energy into adjacent tissue to create a tissue pocket therein.

- 1 121. A method according to Claim 120 wherein the energy emitting apparatus is
- 2 a radiofrequency electrode and wherein the step of using the tissue pocket creating
- 3 apparatus comprises causing the electrode to emit energy of a magnitude and
- 4 duration sufficient to create the tissue pocket.

- 1 122. A method according to Claim 120 wherein the energy emitting apparatus is
- 2 a laser.

- 1 123. A method according to Claim 119 wherein the tissue pocket creating
- 2 apparatus comprises a nozzle through which a stream of fluid may be injected and
- 3 wherein the step of using the tissue pocket creating apparatus comprises injecting
- 4 fluid through the nozzle to create the pocket in adjacent tissue.

- 1 124. A method according to Claim 119 wherein the tissue pocket creating
- 2 apparatus comprises an expandable cage and wherein the step of using the tissue
- 3 pocket creating apparatus comprises expanding the cage to create the pocket in
- 4 adjacent tissue.

- 1 125. A method according to Claim 61 wherein the second apparatus is an
- 2 elongate member that comprises a therapeutic apparatus operative to deliver a
- 3 therapy to the target site and wherein the method further comprises the step of:
- 4 (F) using the therapeutic apparatus to deliver therapy to the target site.

- 1 126. A system for delivery of a substance to a target site located a spaced
- 2 distance from a blood vessel within the body of a human or animal patient, said
- 3 system comprising:
 - 4 a vessel wall penetrating catheter that has a vessel wall penetrator
 - 5 advanceable therefrom, said vessel wall penetrating catheter being insertable into
 - 6 the vasculature and positionable in the blood vessel near the target site and said
 - 7 penetrator being thereafter advanceable from the catheter and through the wall of
 - 8 the blood vessel in the direction of the target site;

9 a delivery catheter that is advanceable through the penetrator and to the
10 target site, said delivery catheter being of sufficient length and constructed such
11 that, after the delivery catheter has been advanced through the penetrator and to
12 the target site, the penetrator may be retracted into the vessel wall penetrating
13 catheter and the vessel wall penetrating catheter may be removed, leaving the
14 delivery catheter in place such that the delivery catheter extends through the
15 patient's vasculature into the blood vessel near the target site, outwardly through
16 the wall of the blood vessel and to the target site.

1 127. A system according to Claim 126 wherein the delivery catheter comprises
2 a hub member that is a) not attached to the proximal end of the delivery catheter
3 while the vessel wall penetrating catheter is being withdrawn and removed and b)
4 attached to the proximal end of the delivery catheter after the vessel wall
5 penetrating catheter has been withdrawn and removed.

1 128. A system according to Claim 126 wherein the delivery catheter further
2 comprises at least one anchoring element for holding the delivery at the target site.

1 129. A system according to Claim 127 wherein the delivery catheter further
2 comprises a barrier for deterring substances injected through the delivery catheter
3 from backflowing around the delivery catheter through the tissue tract through
4 which the delivery catheter extends from the blood vessel to the target site.

1 130. A system according to Claim 126 wherein the delivery catheter further
2 comprises apparatus for preventing cellular ingrowth and other matter from
3 obstructing the lumen of the delivery catheter.

1 131. A system according to Claim 126 wherein the vessel wall penetrating
2 catheter further comprises a guidance element that facilitates positioning and
3 orientation of the vessel wall penetrating catheter within the blood vessel such that,
4 then the penetrator is subsequently advanced from the vessel wall penetrating
5 catheter, the penetrator will travel substantially toward the target site.

1 132. A method for delivery of substances or apparatus to a target site located a
2 spaced distance from a blood vessel within the body of a human or animal patient,
3 said method comprising the steps of:

4 (A) Inserting a vessel wall penetrating catheter into the vasculature of the
5 patient, said vessel wall penetrating catheter having a penetrator
6 advanceable therefrom;

7

8 (B) positioning the vessel wall penetrating catheter in the blood vessel
9 near the target site;

10

11 (C) advancing the penetrator from the vessel wall penetrating catheter
12 and through the wall of the blood in the direction of the target site;

13

14 (D) advancing a delivery catheter through the penetrator and to the target
15 site;

16

17 (E) retracting the penetrator into the vessel wall penetrating catheter;
18 and,

19

20 (F) withdrawing and removing the vessel wall penetrating catheter,
21 leaving the delivery catheter indwelling such that it extends through
22 the patient's vasculature into the blood vessel near the target site,
23 outwardly through the wall of the blood vessel and to the target site.

1 133. A method according to Claim 132 wherein the delivery catheter comprises
2 a hub member that is a) not attached to the proximal end of the delivery catheter
3 while the vessel wall penetrating catheter is being withdrawn and removed and b)
4 attached to the proximal end of the delivery catheter after the vessel wall
5 penetrating catheter has been withdrawn and removed, and wherein the method
6 further comprises the steps of:

7 causing the hub member to be detached from the delivery catheter while the
8 vessel wall penetrating catheter is being withdrawn and removed in Step F; and,
9 causing the hub member to be attached to the proximal end of the delivery
10 catheter after the vessel wall penetrating catheter has been withdrawn and
11 removed in Step F .

1 134. A method according to Claim 132 wherein the delivery catheter further
2 comprises at least one anchoring element for holding the delivery at the target site
3 and wherein the method further comprises:

4 causing the anchoring element to hold the delivery catheter at the target site
5 at least after Step F has been performed.

1 135. A method according to Claim 132 wherein the delivery catheter further
2 comprises a barrier for deterring substances injected through the delivery catheter
3 from backflowing around the delivery catheter through the tissue tract through
4 which the delivery catheter extends from the blood vessel to the target site and
5 wherein the method further comprises:

6 causing the barrier to deter substances injected through the delivery catheter
7 from backflowing around the delivery catheter through the tissue tract through
8 which the delivery catheter extends from the blood vessel to the target site

1 136. A system according to Claim 132 wherein the delivery catheter further
2 comprises apparatus for preventing cellular ingrowth and other matter from
3 obstructing the lumen of the delivery catheter and wherein the method further
4 comprises the step of:

5 causing the apparatus for preventing cellular ingrowth and other matter from
6 obstructing the lumen of the delivery catheter to prevent cellular ingrowth or other
7 matter from obstructing the lumen of the delivery catheter .

8 137. A system according to Claim 126 wherein the vessel wall penetrating
9 catheter further comprises a guidance element that facilitates positioning and
10 orientation of the vessel wall penetrating catheter within the blood vessel such that,
11 then the penetrator is subsequently advanced from the vessel wall penetrating

12 catheter, the penetrator will travel substantially toward the target site and wherein
13 the method further comprises the step of:

14 using the guidance element to position and orient the vessel wall penetrating
15 catheter in the blood vessel prior to performance of Step C such that when Step C
16 is subsequently performed, the penetrator will travel through the blood vessel wall
17 substantially in the direction of the target site.

1 138. A system for delivery of a substance or article to an intramyocardial location
2 in the heart of a mammalian patient, said system comprising:

3 a tissue penetrating catheter that is advanceable through the vasculature to
4 a position within a chamber of the heart;

5 a tissue penetrator having a hollow bore extending therethrough, the
6 penetrator being advancable from the tissue penetrating catheter, through the
7 endocardial surface of the heart and into the myocardium; and,

8 a delivery catheter that is advanceable through the bore of the penetrator
9 and into the myocardial tissue;

0 the substance or article being thereby deliverable through the delivery
1 catheter and into at least one intramyocardial site.

1 139. A system according to Claim 139 wherein the tissue penetrating catheter
2 comprises a flexible catheter body having a distal end and a penetrator outlet port
3 located in the distal end of the catheter body.

1 140. A system according to Claim 139 wherein the tissue penetrating catheter
2 comprises a flexible catheter body having a side wall and a penetrator outlet port
3 located in the side wall of the catheter body.

1 141. A system according to Claim 139 wherein, after the penetrator has been
2 advanced into the myocardium and as the delivery catheter is being advanced
3 through the bore of the penetrator, the configuration and position of the penetrator

4 will cause the delivery catheter to advance through myocardial tissue on a path
5 which does not result in the delivery catheter a) entering any chamber of the heart,
6 b) passing outwardly through the epicardial surface of the heart and/or c)
7 perforating a substantially sized coronary blood vessel in a manner that causes
8 clinically significant bleeding or other clinically significant complications.

1 142. A system according to Claim 138 wherein the vessel wall penetrating
2 catheter further comprises iii) a guidance element useable by the operator to
3 position the vessel wall penetrating catheter body within the vasculature of the
4 patient such that when the vessel wall penetrating member is passed from the
5 catheter body it will penetrate through the wall of the blood vessel in the direction
6 of the intended extravascular target site.

1 143. A system according to Claim 142 wherein the guidance element comprises
2 an imaging apparatus.

1 144. A system according to Claim 143 wherein the imaging apparatus is an
2 ultrasound imaging apparatus.

1 145. A system according to Claim 142 wherein the guidance element comprises
2 an imageable marker on the vessel wall penetrating catheter body.

1 146. A system according to Claim 142 wherein the guidance element comprises
2 the combination of an imaging apparatus and at least one imageable marker that
3 is imageable by the imaging apparatus.

1 147. A system according to Claim 142 wherein the guidance element comprises
2 an emitter located on or in the catheter body, said emitter emitting a signal that is
3 received by an extracorporeally situated signal-receiving apparatus.

1 148. A system according to Claim 138 wherein the delivery catheter further
2 comprises a matter blocking member for preventing cellular ingrowth and other
3 matter from obstructing the lumen of the delivery catheter.

1 149. A system according to Claim 148 wherein the delivery catheter has an
2 outflow opening through which substances may pass out of the lumen of the
3 delivery catheter and into the target location and wherein the matter blocking
4 member comprises a selectively permeable barrier that allows desired substances
5 to be infused in the distal direction through the outflow opening and to the target
6 location but prevents cellular ingrowth and other matter from entering the lumen of
7 the delivery catheter through said outflow opening.

1 150. A system according to Claim 149 wherein the selectively permeable barrier
2 is a balloon attached to the delivery catheter such that substances infused through
3 the lumen of the delivery catheter collect within the balloon and subsequently
4 diffuse outwardly through the balloon.

1 151. A system according to Claim 148 wherein the matter blocking member
2 comprises a stylet that is insertable into the lumen of the delivery catheter to block
3 the entry of extraneous matter thereinto.

1 152. A system according to Claim 151 wherein the stylet is removable from the
2 lumen of the delivery catheter to permit delivery of a substance or apparatus
3 through the delivery catheter.

1 153. A system according to Claim 138 wherein the delivery catheter comprises:
2 a first tube having a lumen and a sidewall in which an outflow aperture is
3 formed; and,
4 a second tube rotatably disposed in a coaxial position within the first tube,
5 said second tube having a lumen, a closed distal end and a sidewall in which an
6 opening is formed;

7 the second tube being rotatably moveable between i) a blocking position
8 wherein the side wall of the second tube substantially blocks the outflow aperture
9 of the first tube to prevent cellular ingrowth and other matter from entering the
10 lumen of the second tube and ii) an infusion position wherein the opening of the
11 second tube is aligned with the outflow opening of the first tube such that a
12 substance that is injected into the lumen of the second tube will flow through the
13 opening of the second tube and through the outflow opening of the first tube.

1 154. A system according to Claim 152 wherein a plurality of outflow apertures are
2 formed in the sidewall of the first tube.

1 155. A system according to Claim 138 wherein the delivery catheter comprises:
2 a tube having a lumen and a sidewall in which an outflow aperture is formed;
3 and,
4 an obturator member disposed at least partially within the lumen of the tube,
5 said obturator member being alternately disposable in i) a blocking position wherein
6 the obturator substantially blocks the outflow aperture of the tube to prevent cellular
7 ingrowth and other matter from entering the lumen of the tube and ii) an infusion
8 position wherein the obturator does not substantially block the outflow apertures
9 such that fluid may be injected through the lumen of the tube and out of the outflow
10 aperture.

1 156.—A system according to Claim 155 wherein a plurality of outflow apertures are
2 formed in the sidewall of the tube.

1 157. A system according to Claim 155 wherein the obturator member is an
2 inflatable balloon that assumes said blocking position when inflated and said
3 infusion position when deflated.

1 158. A system according to Claim 138 wherein the delivery catheter comprises
2 an infusion lumen, a return lumen, an outflow aperture through which infused
3 substances may flow out of the infusion lumen and a flow diverter, said flow diverter

4 that is alternately deployable in i) an infusion position whereby substances infused
5 through the infusion lumen will flow out of the outflow aperture and ii) a recirculation
6 position whereby fluid infused through the infusion lumen will be recirculated back
7 through the return lumen.

1 159. A system according to Claim 138 wherein the delivery catheter comprises
2 a pressure increasing outflow opening configured to cause an increase the
3 pressure of fluids that are injected through the delivery catheter lumen and out of
4 said pressure increasing outflow opening.

1 160. A system according to Claim 159 wherein said pressure increasing outflow
2 opening is formed in the side wall of the delivery catheter.

1 161. A system according to Claim 160 wherein a plurality of pressure increasing
2 outflow openings are formed in the side wall of the delivery catheter.

1 162. A system according to Claim 160 wherein the delivery catheter further
2 comprises an anchoring member for anchoring the catheter in a substantially fixed
3 position within the patient's body.

1 163. A system according to Claim 162 wherein the anchoring member is selected
2 from the group of anchoring members consisting of:

3 _____ a hook; _____
4 _____ a barb;
5 _____ a permeable surface into which tissue may grow;
6 _____ an adhesive; and,
7 _____ combinations thereof.

1 164. A system according to Claim 138 wherein the delivery catheter further
2 comprises a backflow deterrent member for blocking backflow of substances that
3 have been injected through the delivery catheter.

- 1 165. A system according to Claim 164 wherein said backflow deterrent member
- 2 comprises a backflow barrier rib formed on the delivery catheter.

- 1 166. A system according to Claim 165 wherein said backflow barrier comprises
- 2 an inflatable balloon on the delivery catheter.

- 1 167. A system according to Claim 165 wherein said backflow barrier comprises
- 2 a raised projection formed on the exterior of the delivery catheter.

- 1 168. A system according to Claim 167 wherein the raised projection comprises
- 2 an annular rib formed about the outer surface of the delivery catheter

- 1 169. A system according to Claim 164 wherein the backflow deterrent comprises
- 2 a sealant that is implanted prior to or concurrently with removal of the delivery
- 3 catheter so as to prevent the injected substance from bacflowing through the tract
- 4 from which the delivery catheter is removed.

- 1 170. A system according to Claim 169 wherein the sealant comprises a quantity
- 2 of a flowable sealant injected into the tract upon removal of the delivery catheter.

- 1 171. A system according to Claim 169 wherein the sealant comprises a
- 2 detachable sealing member.

- 1 172. A system according to Claim 171 wherein the detachable sealing member
- 2 is formed of biodegradable material.

- 1 173. A system according to Claim 172 wherein the sealing member is a collagen
- 2 sponge.

- 1 174. A system according to Claim 172 wherein the sealing member is a hydrogel
- 2 sponge.

- 1 175. A system according to Claim 138 wherein at least a portion of the delivery
- 2 catheter is coated with an adhesive.
- 1 176. A system according to Claim 138 wherein an anti-microbial substance is
- 2 disposed on at least a portion of the delivery catheter.
- 1 177. A system according to Claim 138 wherein an anti-coagulant substance is
- 2 disposed on at least a portion of the delivery catheter.
- 1 178. A system according to Claim 138 further comprising apparatus for creating
- 2 a pocket within tissue adjacent to the delivery catheter such that when a substance
- 3 or apparatus is introduced through the delivery catheter it will be received within
- 4 said pocket.
- 1 179. A system according to Claim 178 wherein the apparatus for creating a
- 2 pocket comprises an energy emitting member that emits energy into adjacent tissue
- 3 to create said pocket.
- 1 180. A system according to Claim 179 wherein the energy emitting apparatus is
- 2 a radiofrequency electrode.
- 1 181. A system according to Claim 179 wherein the energy emitting apparatus is
- 2 a laser.
- 1 182. A system according to Claim 178 wherein the apparatus for creating a
- 2 pocket comprises a nozzle through which a stream of fluid may be injected to
- 3 create the pocket in adjacent tissue.
- 1 183. A system according to Claim 178 wherein the apparatus for creating a
- 2 pocket comprises an expandable cage which, when expanded, creates said pocket.
- 3

- 1 184. A system according to Claim 138 further in combination with an infusion
- 2 apparatus for infusing a substance through the delivery catheter.

- 1 185. A system according to Claim 184 wherein said infusion apparatus is a
- 2 syringe.

- 1 186. A system according to Claim 184 wherein said infusion apparatus is a pump.

- 1 187. A system according to Claim 184 wherein said infusion apparatus is a
- 2 reservoir positioned for gravity drainage of the substance through the delivery
- 3 catheter.

- 1 188. A system according to Claim 184 wherein said infusion apparatus further
- 2 comprises a quantity of a substance for infusion through the delivery catheter.

- 1 189. A system according to Claim 188 wherein the substance is a drug.

- 1 190. A system according to Claim 189 wherein the drug is selected from the
- 2 group consisting of: thrombolytics, platelet inhibitors, anti-restenotic agents, beta
- 3 adrenergic blockers, ion channel antagonists, positive or negative ionotropic
- 4 agents, anti-arrhythmics and combinations thereof.

- 1 191. A system according to Claim 188 wherein the substance is a protein.

- 1 192. A system according to Claim 188 wherein the substance is an angiogenic
- 2 substance.

- 1 193. A system according to Claim 191 wherein the angiogenic substance is
- 2 selected from the group consisting of vascular endothelial growth factor (VEGF),
- 3 fibroblast growth factors (FGF), epidermal growth factor (EGF), platelet-derived
- 4 growth factor (PDGF), hepatocyte growth factor (HGF) or scatter factor, heparin
- 5 combined with an adenosine receptor agonist, and combinations thereof.

- 1 194. A system according to Claim 188 wherein the substance comprises cells.
- 1 195. A system according to Claim 194 wherein the substance comprises
2 progenitor cells for a type of cell that is desired to be formed at the target site.
- 1 196. A system according to Claim 195 wherein said substance comprises
2 myoblasts to form cardiac muscle cells.
- 1 197. A system according to Claim 196 wherein said cells are selected from the
2 group consisting of stem cells, progenitor cells, myoblasts, myocytes, secretory
3 cells, pancreatic islet cells, dopamine secreting cells, endothelial cells, hepatocytes,
4 cloned cells, cells grown in cell culture, genetically modified cells, and combinations
5 thereof.
- 1 198. A system according to Claim 188 wherein the substance is a gene.
- 1 199. A system according to Claim 198 wherein the substance comprises a gene
2 and a vector for facilitating entry of the gene into locations within cells at which the
3 gene will have a desired effect on the cells.
- 1 200. A system according to Claim 199 wherein the vector is a virus.
- 1 201. A system according to Claim 138 wherein the penetrator is of a helical
2 configuration and is capable of being rotated as it is advanced into the myocardial
3 tissue.
- 1 202. A method for delivering a substance or article to one or more intramyocardial
2 sites in the heart of a mammalian patient, the method comprising the steps of:
3 A. providing a tissue penetrating catheter system that comprises i) a
4 catheter that is advanceable through the vasculature to a position within a chamber
5 of the heart, ii) a tissue penetrator having a hollow bore extending therethrough, the

1 penetrator being advancable from the tissue penetrating catheter, and iii) a delivery
2 catheter that is advanceable through the bore of the penetrator and out of the
3 penetrator into myocardial tissue;

4 B. inserting the tissue penetrating catheter into the patient's vasculature
5 and advancing the catheter to a position where the location on the catheter from
6 which the tissue penetrator advances is located within a chamber of the patient's
7 heart;

8 C. advancing the tissue penetrator from the catheter, through the
9 endocardium and into the myocardium;

10 D. advancing the delivery catheter through the bore of the penetrator and
11 into the myocardial tissue; and,

12 E. delivering the substance or article though the delivery catheter and
13 into said one or more intramyocardial sites.

1 203. A method according to Claim 202 wherein the penetrator is curved and
2 wherein Step C further comprises advancing the curved penetrator to a position
3 within the myocardium such that subsequent performance of Step D will not cause
4 the delivery catheter to a) enter any chamber of the heart, b) pass outwardly
5 through the epicardial surface of the heart and/or c) perforate any substantially
6 sized coronary blood vessel in a manner that causes clinically significant bleeding
7 or other clinically significant complications.

1 204.—A method according to Claim 203 wherein the penetrator is helically shaped
2 and wherein Step C further comprises rotating the penetrator.

1 205. A method according to Claim 203 further comprising the steps of:

2 F. retracting the delivery catheter into the bore of the penetrator;

3 G. repositioning the penetrator;

4 H. readvancing the delivery catheter through the bore of the repositioned
5 penetrator and into the myocardium; and,

6 I. delivering the substance or article though the delivery catheter and
7 into said one or more additional intramyocardial sites that are different from the one

1 or more intramyocardial sites into which the substance or article was delivered in
2 Step E.

1 206. A method according to Claim 205 wherein Steps F through G are repeated
2 a plurality of times.

1 207. A method according to Claim 203 wherein Steps D and E further comprise
2 advancing the delivery catheter while periodically injecting the substance or article
3 so as to deliver the substance or article into a plurality of spaced-apart
4 intramyocardial sites.

1 208. A method according to Claim 203 wherein Step E further comprises
2 retracting the delivery catheter while periodically injecting the substance or article
3 so as to deliver the substance or article into a plurality of spaced-apart
4 intramyocardial sites.

1 209. A method according to Claim 203 wherein Steps D and E further comprise
2 advancing the delivery catheter while substantially continually injecting the
3 substance or article so as to deliver a trail of the substance or article within the
4 myocardial tissue.

1 210. A method according to Claim 203 wherein Step E further comprises
2 retracting the delivery catheter while substantially continually injecting the
3 substance or article so as to deliver a trail of the substance or article within the
4 myocardial tissue.

1 211. A method according to Claim 203 wherein the penetrating catheter further
2 comprises a guidance element useable by the operator to position the penetrating
3 catheter body within the chamber of the heart vasculature of the heart such that
4 when the penetrator is advanced from the catheter body it will penetrate through the

1 endocardial surface and into the myocardium, and wherein Step C further
2 comprises using said guidance element to position the penetrating catheter body
3 within the chamber of the heart such that when the penetrator is advanced from the
4 catheter body it will penetrate through the endocardium and into the myocardium.
5

1 212. A method according to Claim 211 wherein the guidance element comprises
2 an imaging apparatus and wherein Step C further comprises using the imaging
3 apparatus to image at least one anatomical marker and using such image to guide
4 the positioning of catheter such that the penetrator will enetr the desired location
5 of the myocardium.

1 213. A method according to Claim 212 wherein the imaging apparatus is an
2 ultrasound imaging apparatus and the image used in Step C is an ultrasound
3 image.

1 214. A method according to Claim 211 wherein the guidance element comprises
2 indicia that indicates the path that will be followed by the penetrator when it is
3 subsequently advanced from the catheter and wherein Step C further comprises
4 obtaining an image of the imageable marker and using such image to guide the
5 positioning of the penetrating catheter.

1 215. A method according to Claim 211 wherein the guidance element comprises
2 the combination of an imaging apparatus and at least one imageable marker on the
3 penetrating catheter, and wherein Step C further comprises using the imaging
4 apparatus to obtain an image of at least the imageable marker and using that
5 image to guide the positioning of the penetrating catheter.

1 216. A method according to Claim 215 wherein the imageable marker provides
2 an indication of the direction in which the penetrator will advance and wherein Step
3 C further comprises imaging of the imageable marker to obtain an indication of the
4 direction in which the penetrator will advance and using said indication to

5 rotationally orient the penetrating catheter such that subsequent advancement of
6 the penetrator will cause the penetrator to travel in the direction of a desired
7 intramyocardial site.

1 217. A method according to Claim 211 wherein the guidance element comprises
2 an emitter located on or in the catheter body, said emitter emitting a signal that is
3 received by an extracorporeally situated signal-receiving apparatus and wherein
4 Step C further comprises using an extracorporeally situated signal-receiving
5 apparatus to receive a signal from the emitter and to thereby guide the placement
6 of the penetrating catheter.

1 218. A method according to Claim 203 wherein the system provided in Step A
2 further comprises a guide catheter through which the penetrating catheter is
3 advanceable and wherein, prior to performance of Step B, the method further
4 comprises the step of:

5 inserting the guide catheter into the patient's vasculature and advancing the
6 guide catheter to a location within a chamber of the heart, and,

7 wherein Step B further comprises inserting the tissue penetrating catheter
8 into the patient's vasculature and advancing the tissue penetrating catheter through
9 the guide catheter to a position where the location on the tissue penetrating
10 catheter from which the tissue penetrator advances is located within a chamber of
11 the patient's heart.

1 219. A system according to Claims 1 or 126 wherein the delivery catheter further
2 comprises a position indicator for indicating the position of the delivery catheter
3 within tissue.

1 220. A system according to Claim 219 wherein the position indicator comprises
2 a radiographically visible marker.

- 1 221. A method according to Claims 61 or 202 wherein the delivery catheter further
2 comprises a position indicator for indicating the position of the delivery catheter
3 within tissue and wherein the method further comprises the step of:
4 using the position indicator to discern the position of the delivery catheter
5 within the patient's body at at least one time during the procedure.

- 1 222. A method according to Claim 221 wherein the position indicator comprises
2 a radiographically visible marker and wherein the step of using the position indicator
3 to discern the position comprises using a radiographic imaging apparatus to discern
4 the location of the radiographically visible marker.

- 1 223. A method according to Claims 61 or 202 wherein the method comprises
2 advancing a delivery catheter through the penetrator and injecting a substance
3 though the delivery catheter.

- 1 224. A method according to Claim 223 wherein the method further comprises
2 moving the delivery catheter while injecting the substance.

- 1 225. A method according to Claim 224 wherein the delivery catheter is advanced
2 while injecting the substance.

- 1 226. A method according to Claim 224 wherein the delivery catheter is retracted
2 while injecting the substance.

- 1 227. A method according to Claim 224 wherein the substance is injected
2 continuously while the delivery catheter is moved to deposit the substance over an
3 elongate area or deposition.

- 1 228. A method according to Claim 224 wherein boluses of the substance are
2 injected at different times while the delivery catheter is moved to provide a plurality
3 of discrete deposits of the substance at different locations on the path over which
4 the delivery catheter was moved.

- 1 229. A method according to Claims 61 or 202 further comprising the steps of:
2 obtaining a quantity of tissue or cellular matter for use as a tissue graft; loading the
3 tissue graft into the delivery catheter; advancing the delivery catheter to an
4 interstitial site; and, delivering the tissue graft through the delivery catheter to the
5 interstitial site.
- 1 230. A method according to Claims 61 or 202 wherein a delivery catheter is
2 advanced through the penetrator and to a location adjacent to an anatomical cavity,
3 chamber or structure that the operator does not wish to penetrate with the delivery
4 catheter and, wherein at least one of the penetrator and delivery catheter are of
5 curved configuration such that the delivery catheter will advance through tissue on
6 a path of advancement that is not directed into the anatomical cavity, chamber or
7 structure that the operator does not wish to penetrate.
- 1 231. A method according to Claim 230 wherein the delivery catheter is advanced
2 into myocardial tissue adjacent to a chamber of the heart and at least one of the
3 penetrator and delivery catheter are of a curved configuration that causes the
4 delivery catheter to be advanced on a path of advancement that is generally
5 tangential to the adjacent chamber of the heart, the delivery catheter being thereby
6 advanced into the myocardial tissue without entering the chamber of the heart.

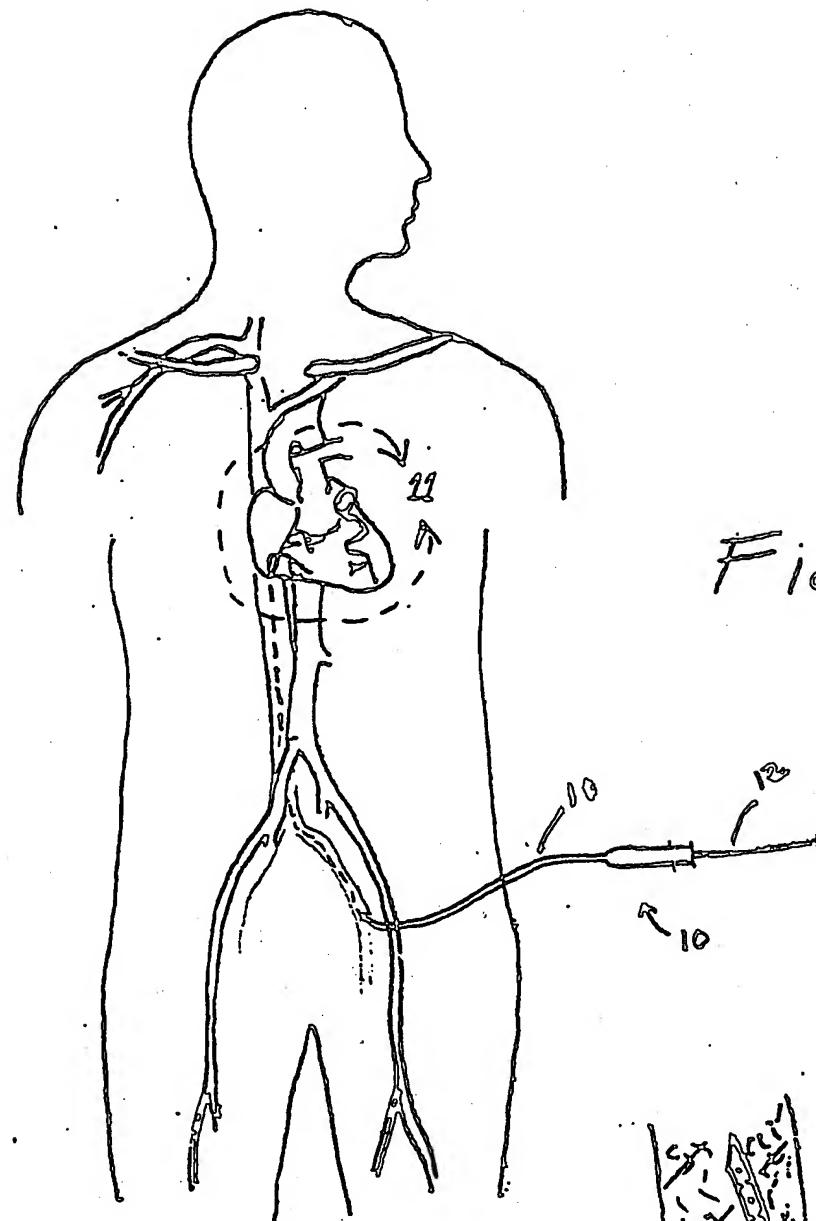


Fig. 1

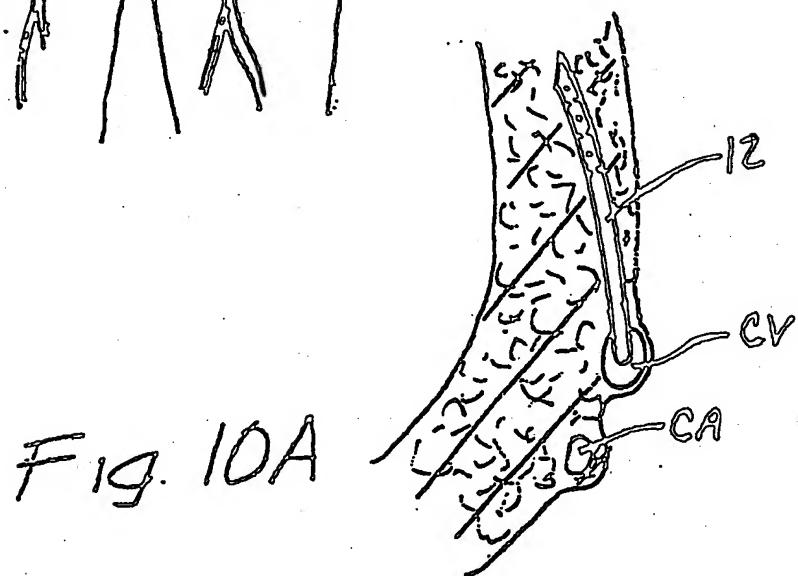
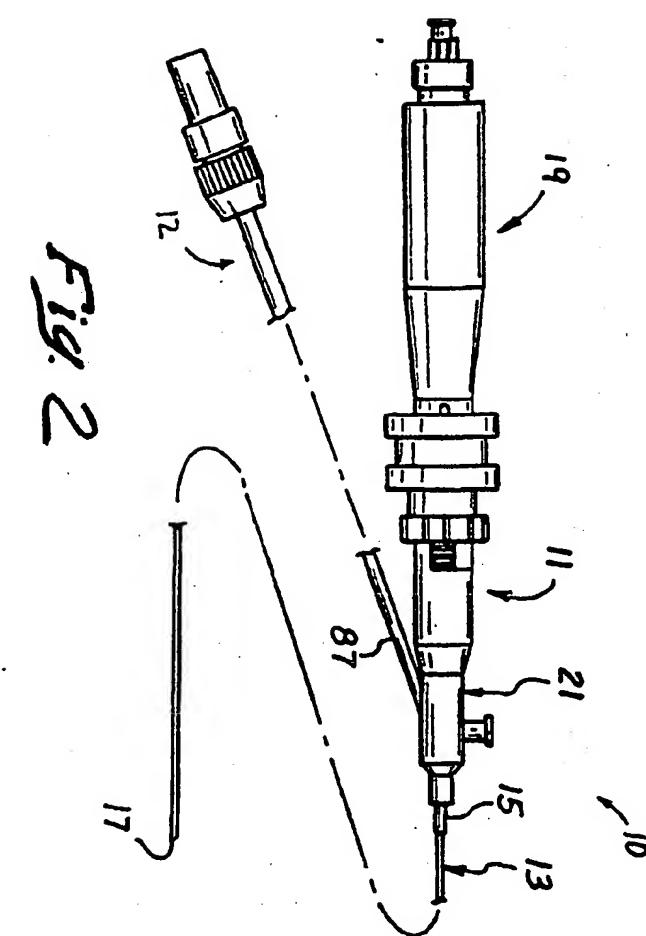
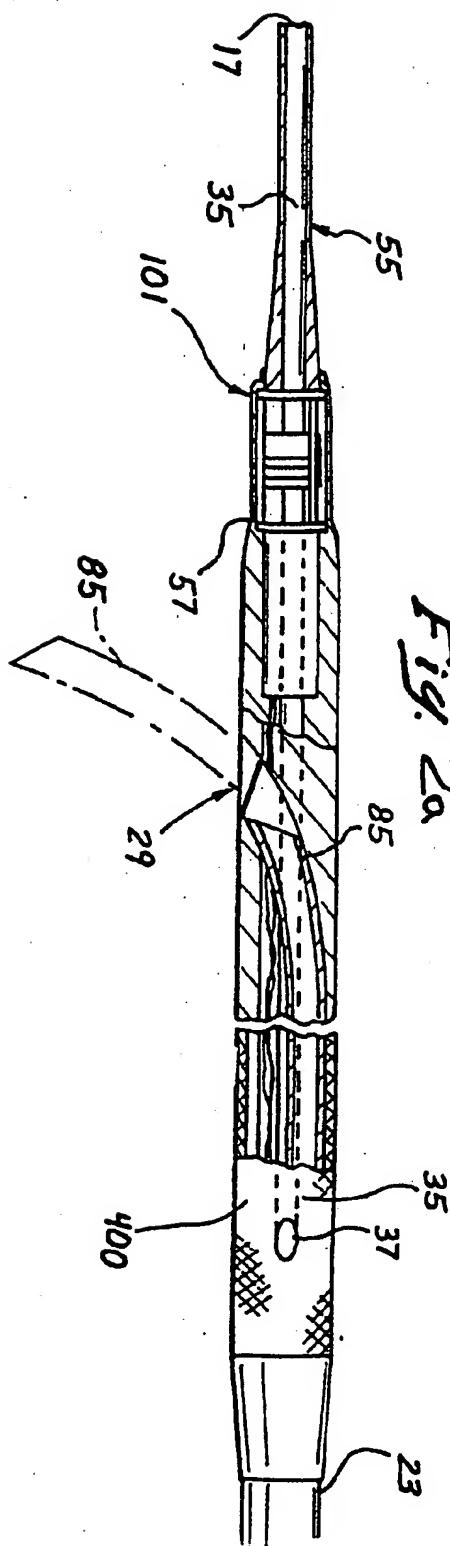


Fig. 10A



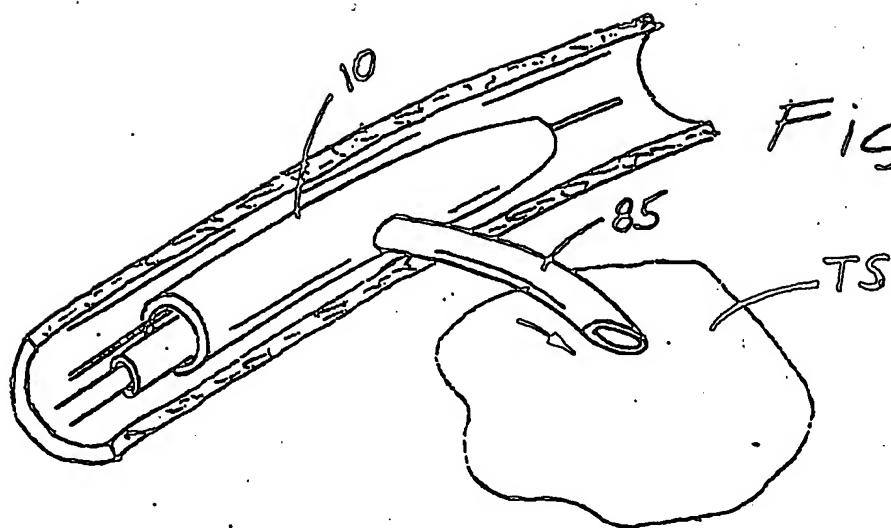


Fig. 2b

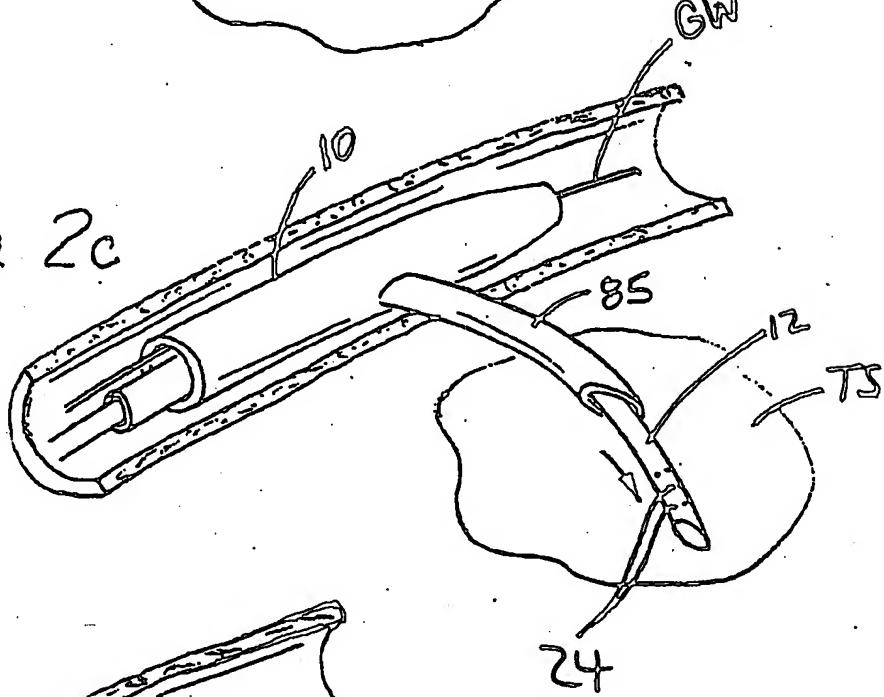


Fig 2c

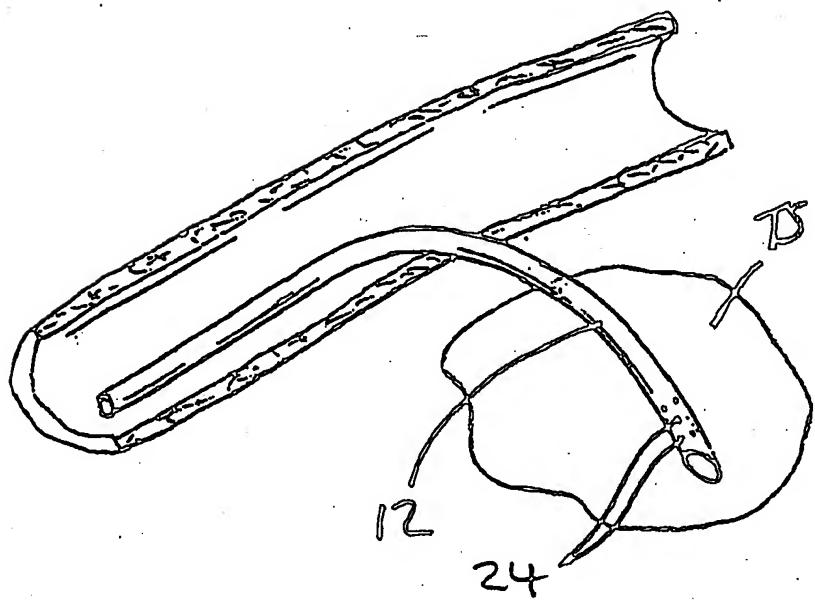
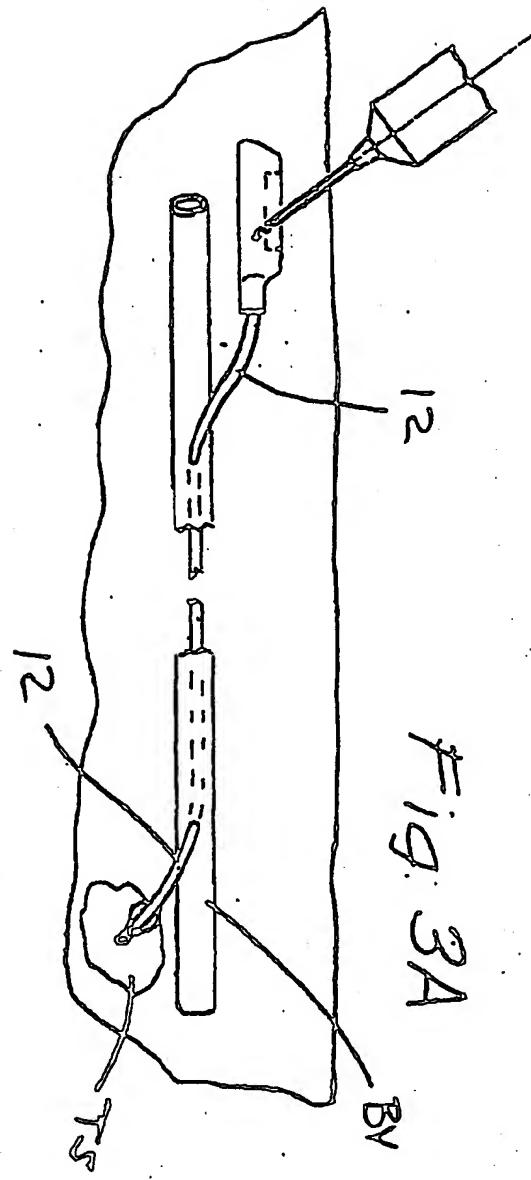
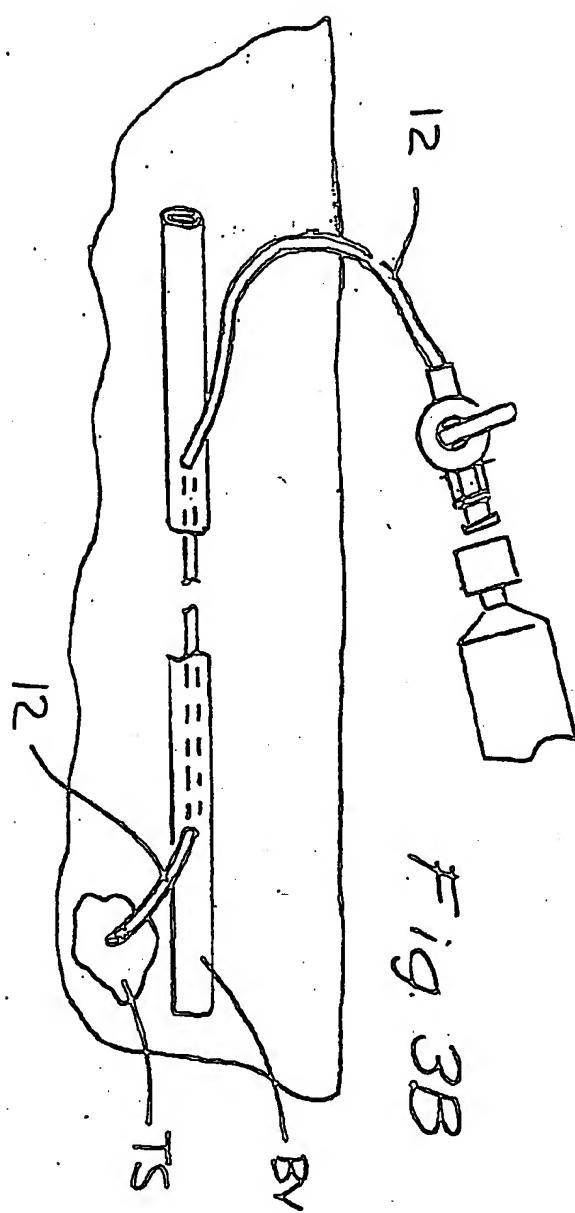
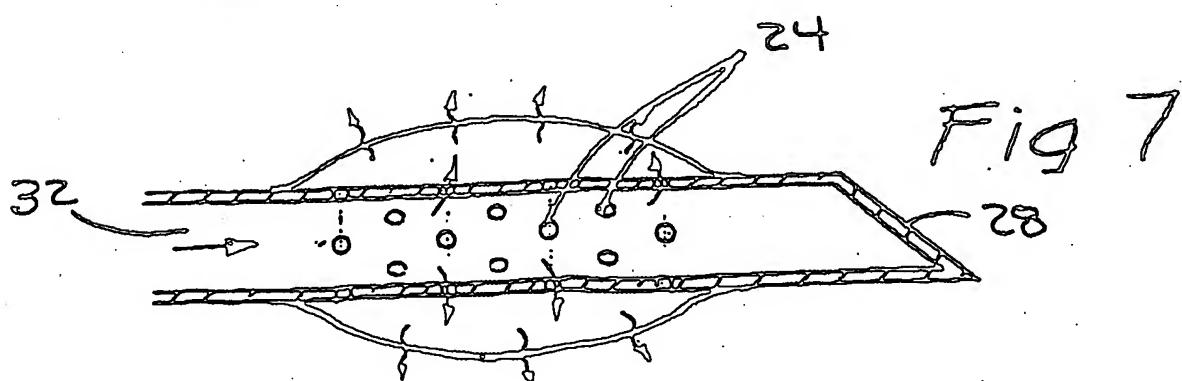
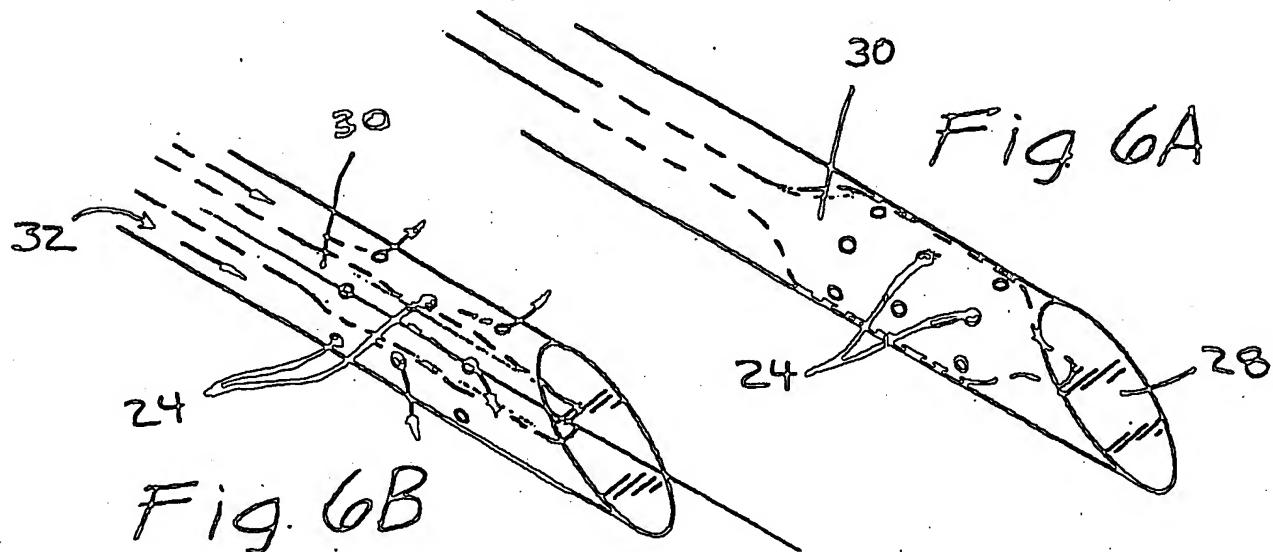
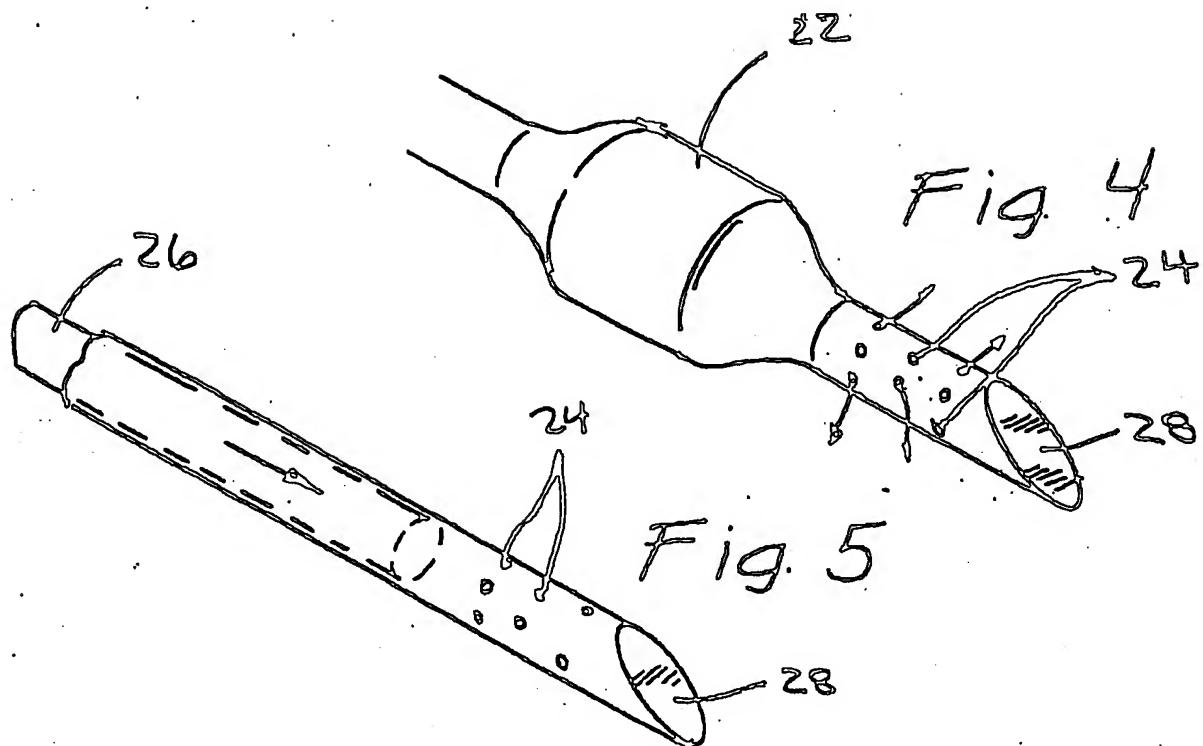


Fig. 2d





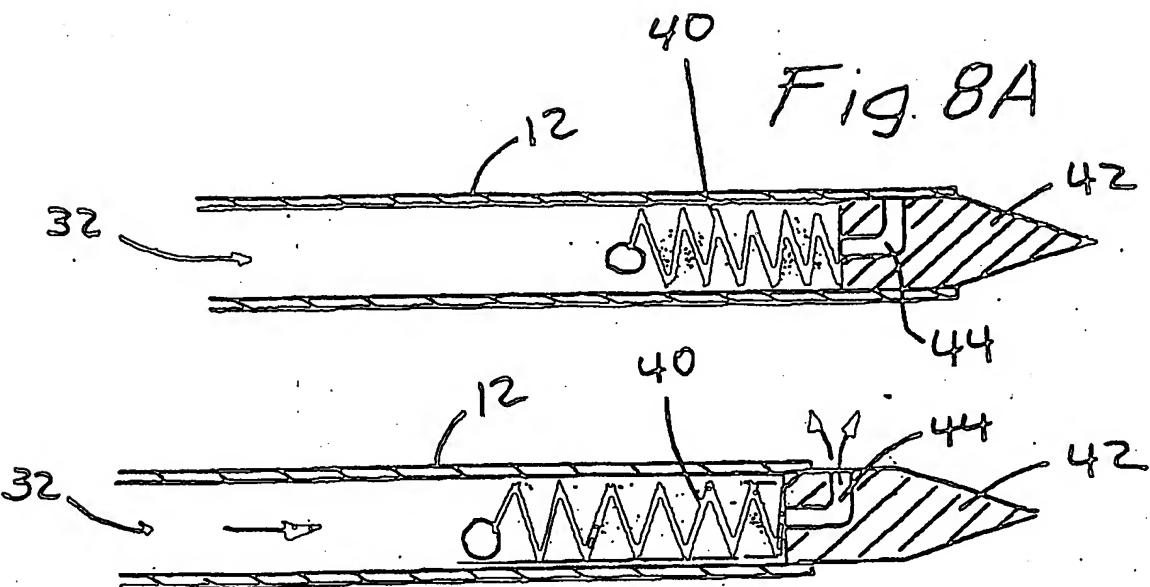


Fig. 8B

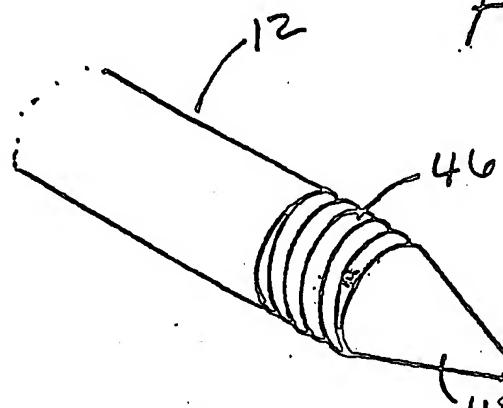
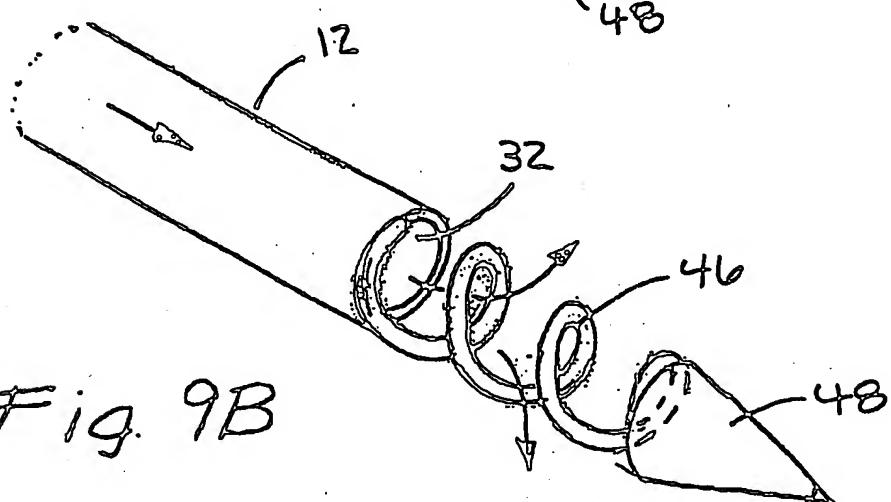


Fig. 9A



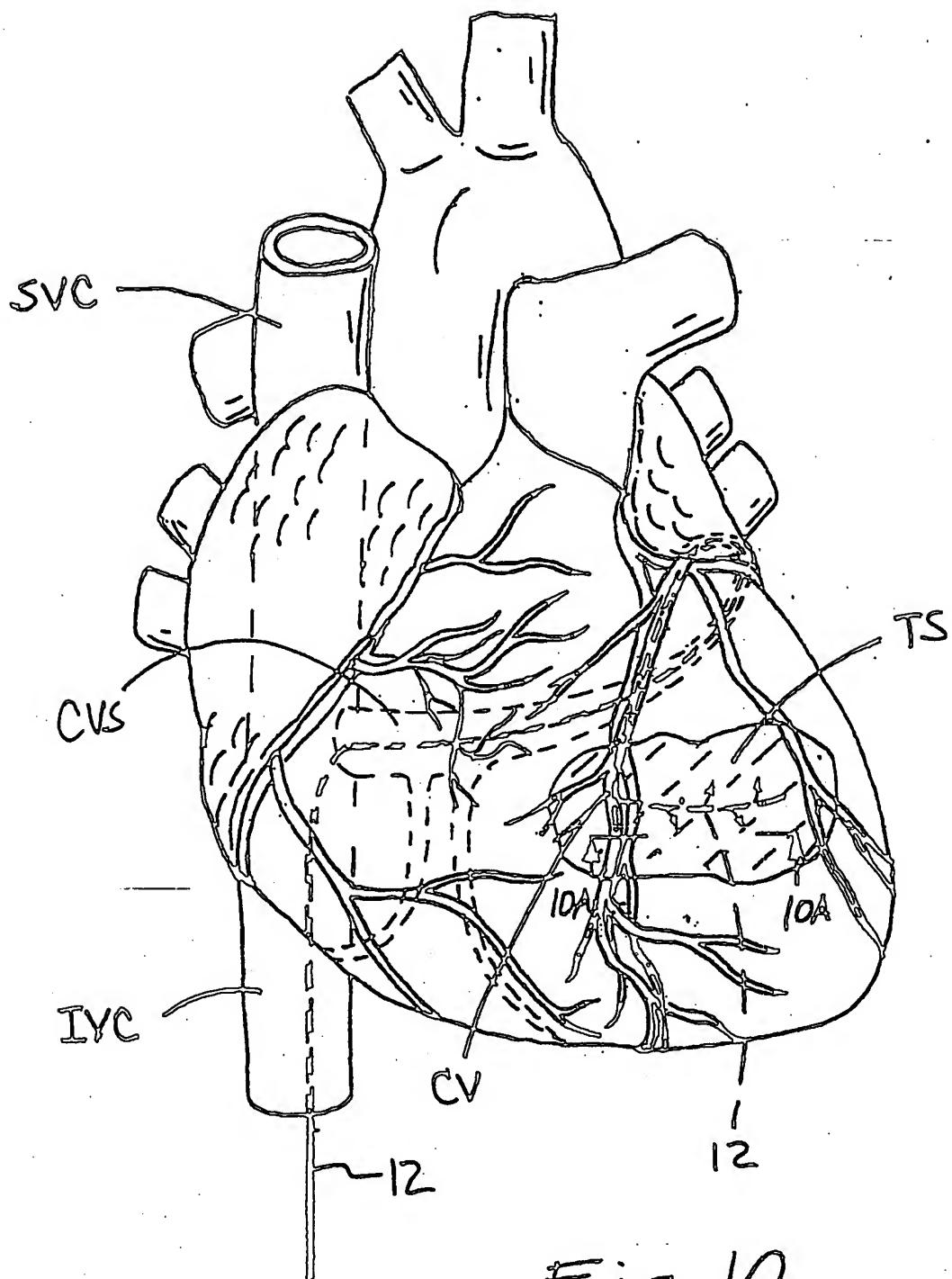


Fig. 10

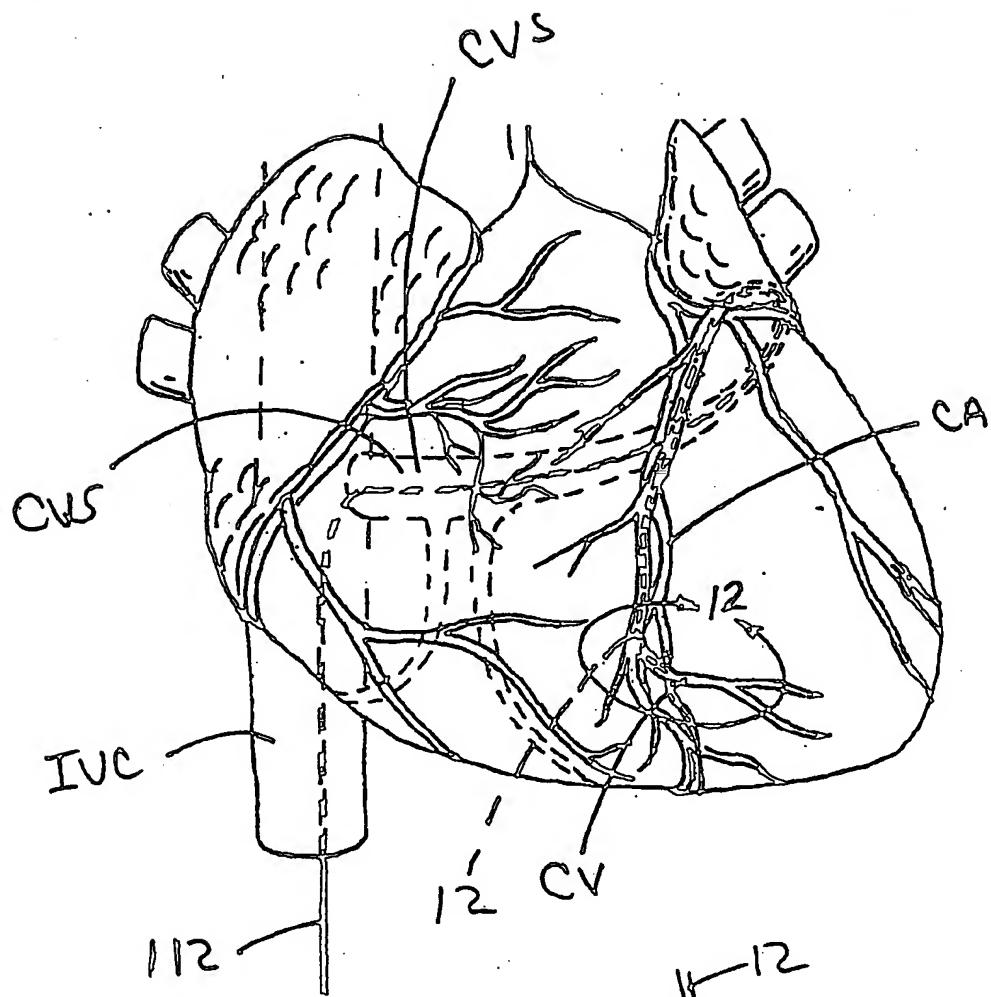


Fig. 11

Fig. 12

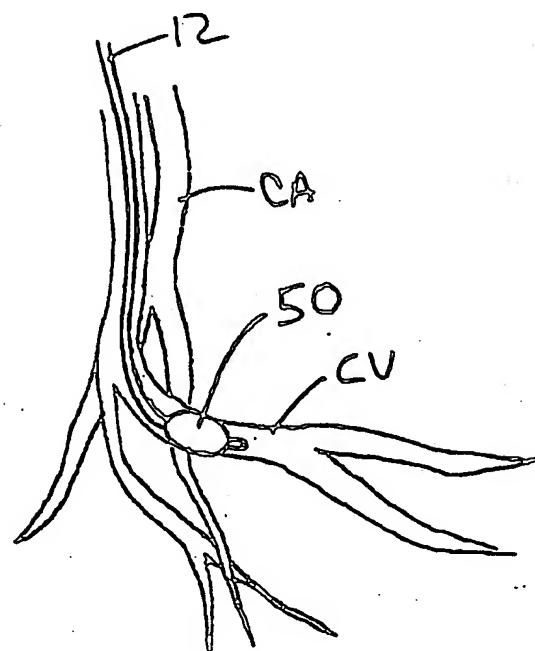
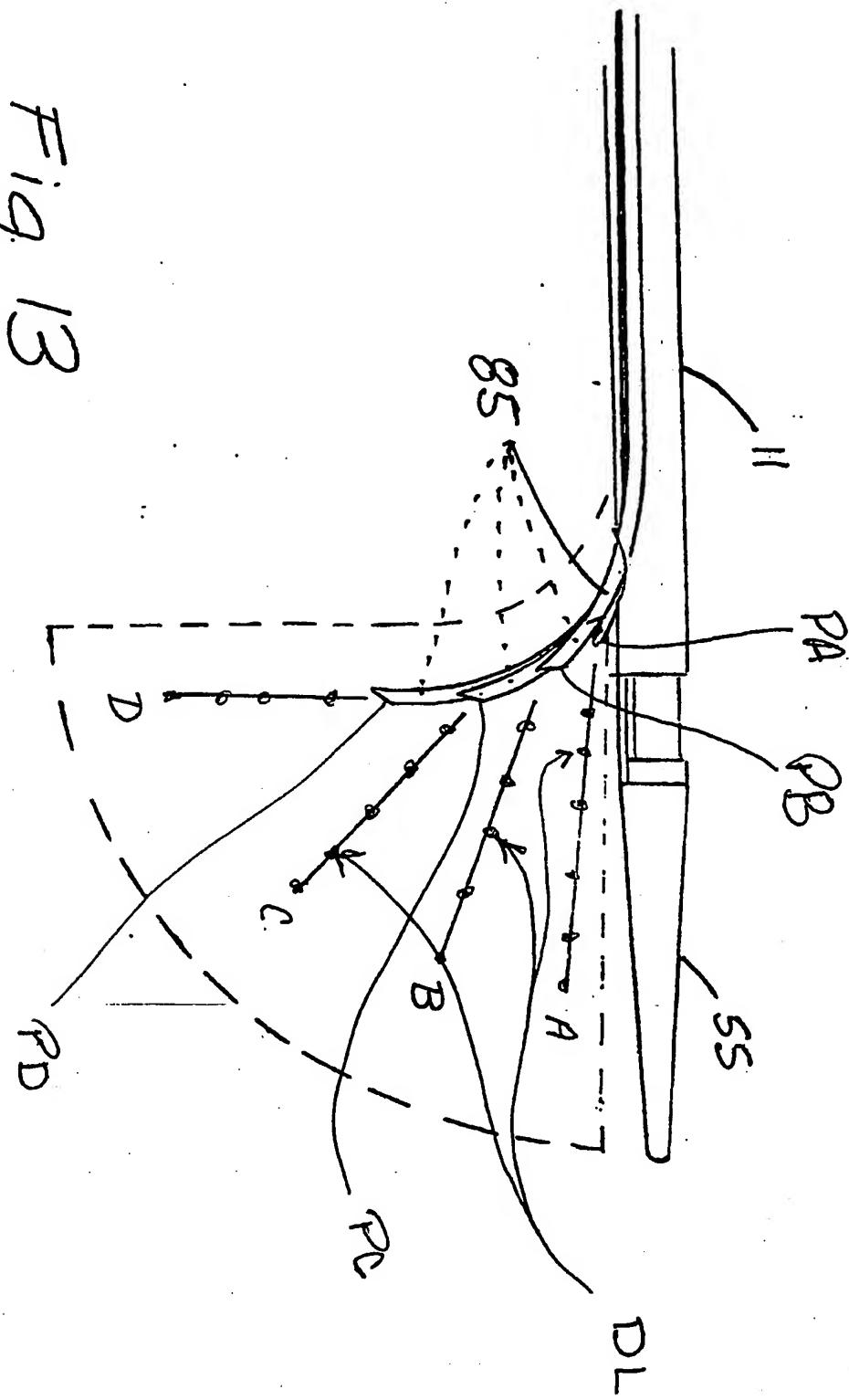


Fig. 13



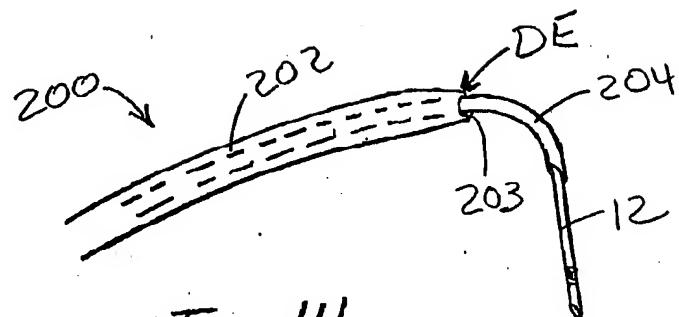


Fig 14

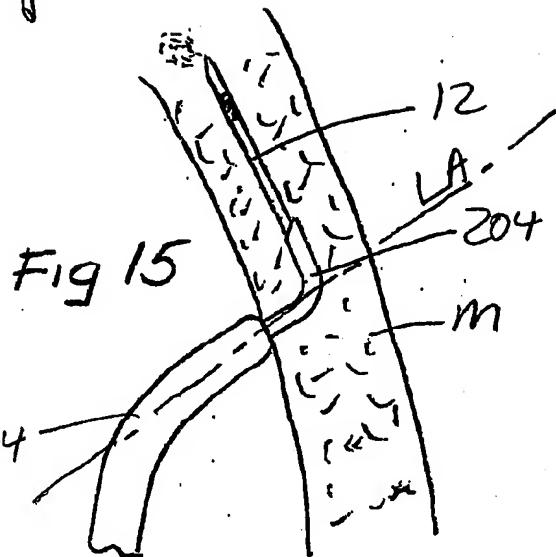


Fig 15

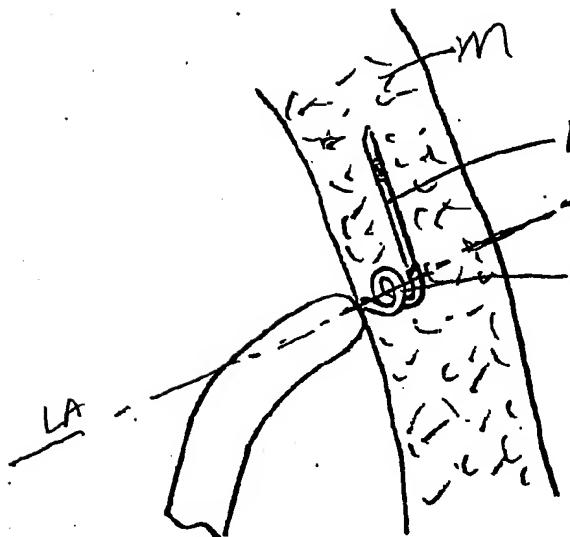


Fig 16

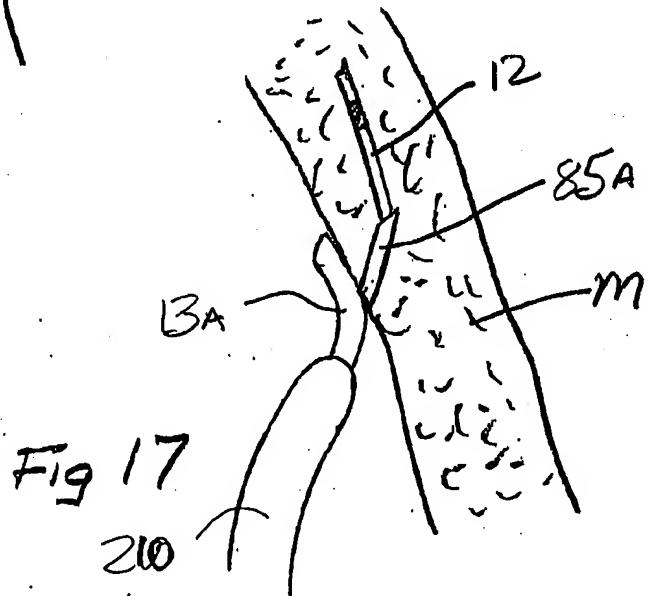


Fig 17

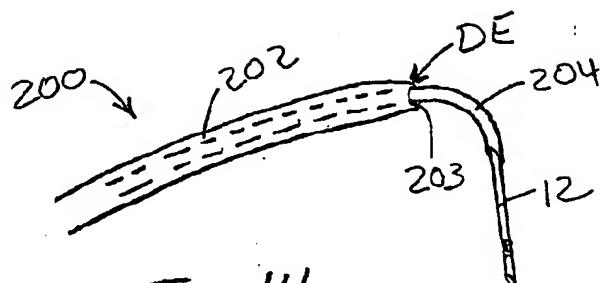


Fig. 14

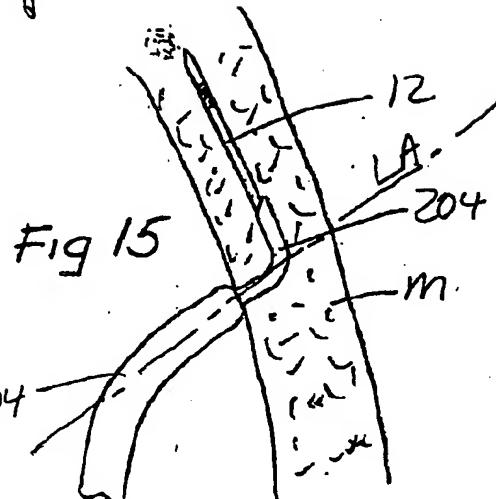
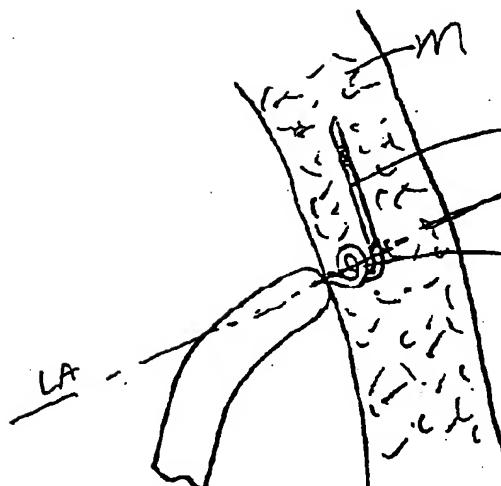


Fig. 15

Fig. 16

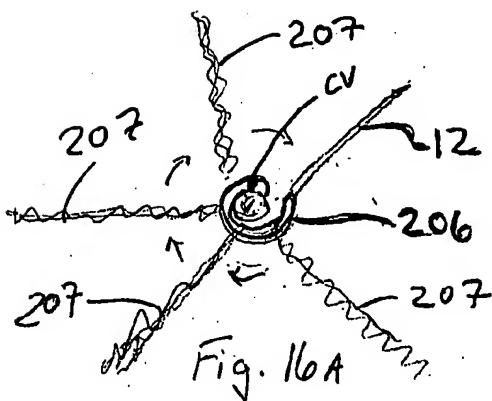


Fig. 16A

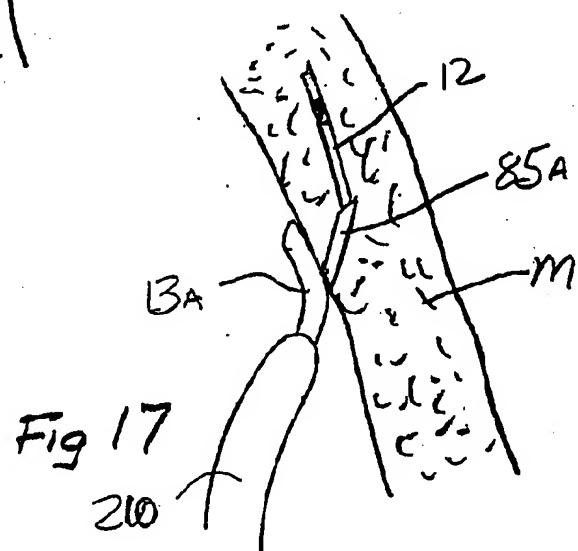


Fig. 17

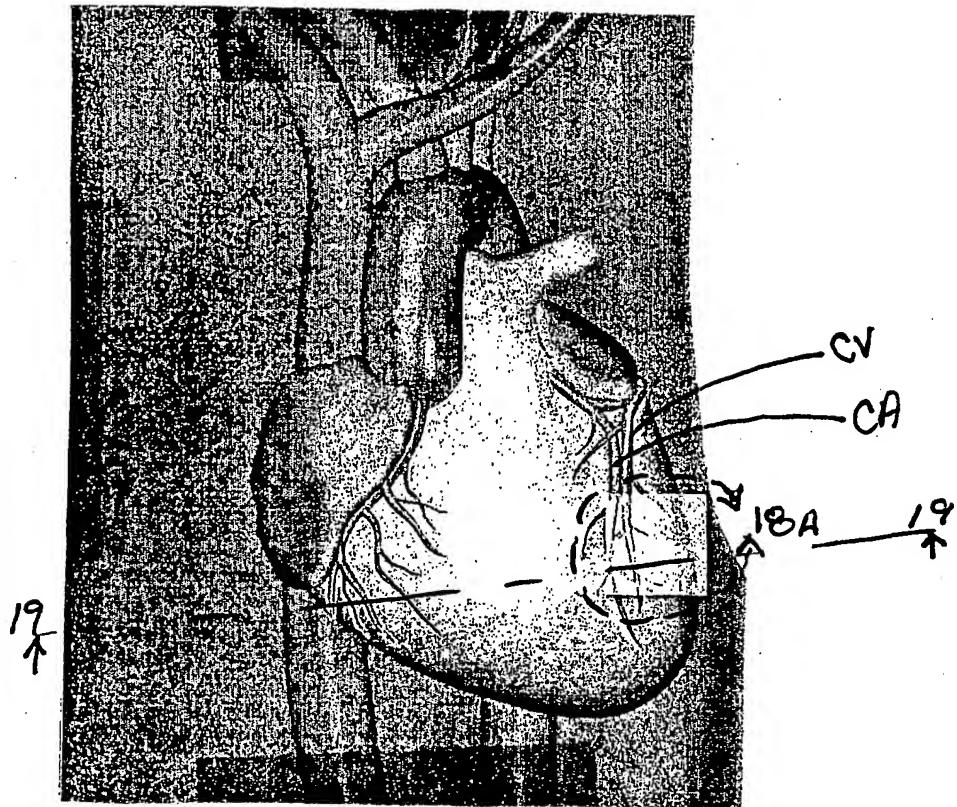


Fig. 18

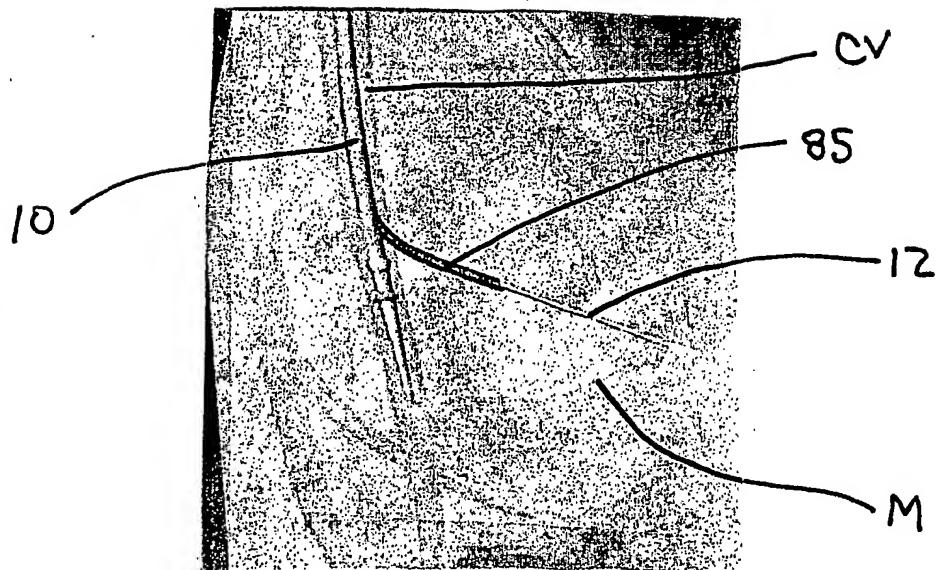
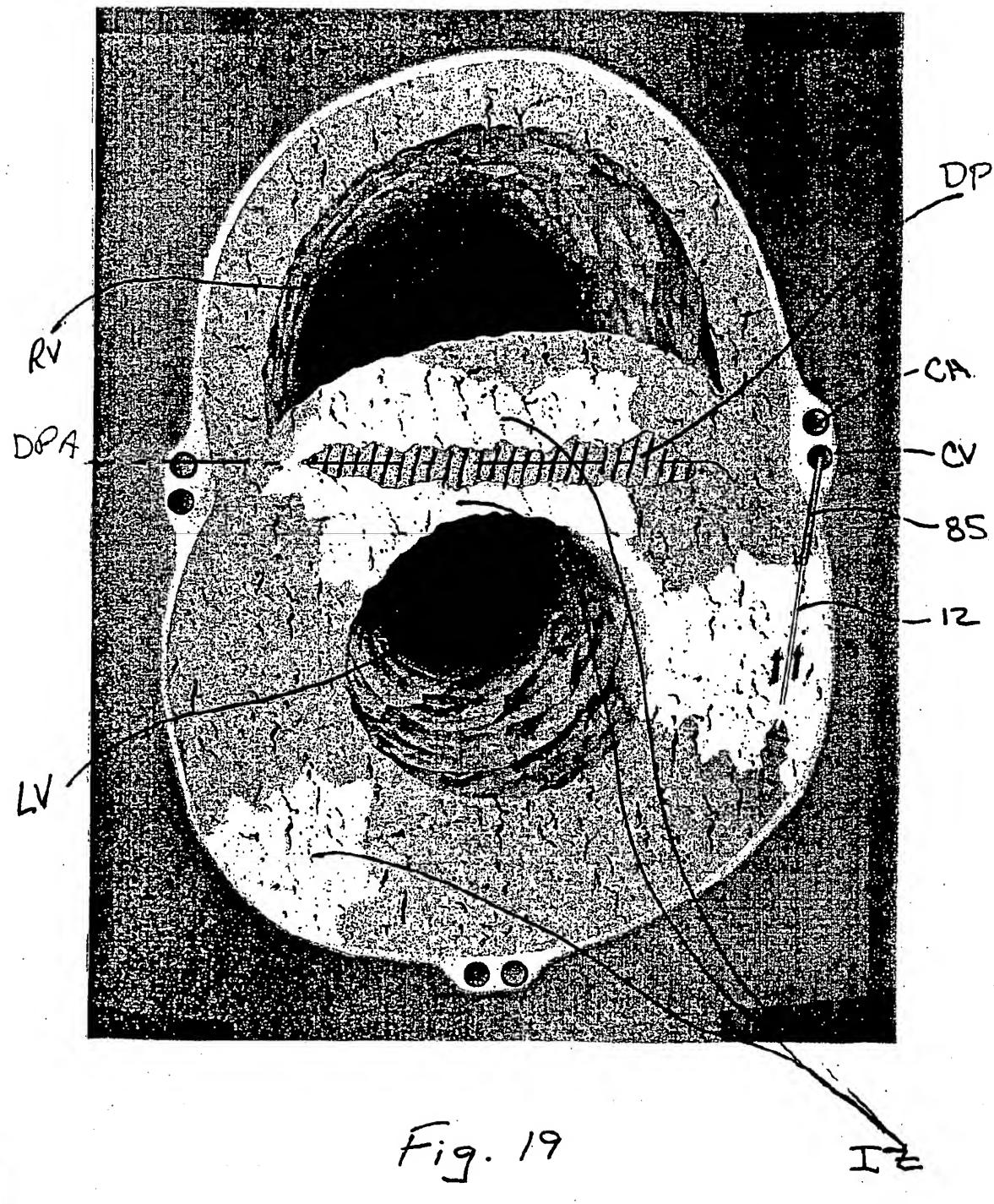


Fig. 18A



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Woodwide Road # 9, Redwood City, CA 94061 (US).
THOLFSEN, David, R. [US/US]; 263 Cresent Ave, San
Francisco, CA 94110 (US).

(21) International Application Number: PCT/US02/01168

(74) Agent: BUYAN, Robert, D.; Stout, Uxa, Buyan &
Mullins LLP, 4 Venture, Suite 300, Irvine, CA 92618 (US).

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(71) Applicant (for all designated States except US):
TRANSVASCULAR, INC. [US/US]; 1505-D Adams
Drive, Menlo Park, CA 94025 (US).

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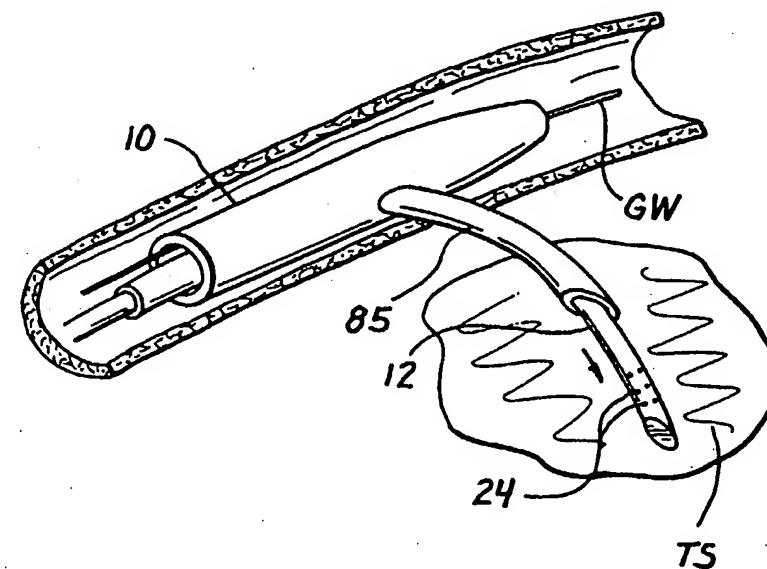
(72) Inventors; and

(75) Inventors/Applicants (for US only): MAKOWER,
Joshua [US/US]; 450 Tyndall Street, Los Altos, CA 94022
(US). LAMSON, Theodore, C. [US/US]; 2172 Camino
Brazos, Pleasanton, CA 94566 (US). FLAHERTY, J.,
Christopher [US/US]; 242 Ipswich Road, Topsfield, MA
01983 (US). REGGIE, John, A. [US/US]; 1145 Amarillo
Ave. #15, Palo Alto, CA 94303 (US). CHANG, John,
Y. [US/US]; 13080 Lorene Court, Mountain View, CA
94040 (US). CANTANESE, III., Joseph [US/US]; 1963

(88) Date of publication of the international search report:
3 April 2003

[Continued on next page.]

(54) Title: DEVICES, SYSTEMS AND METHODS FOR ACUTE OR CHRONIC DELIVERY OF SUBSTANCES OR APPARATUS TO EXTRAVASCULAR TREATMENT SITES



(57) Abstract: Methods and apparatus for delivery of substances or apparatus to target sites. A vessel wall penetrating catheter (11) is inserted into the vasculature, positioned and oriented with a blood vessel near the target extravascular site and a penetrator (85) is advanced from the catheter so as to penetrate outwardly through the wall of the blood vessel in the direction of the target site. Thereafter, a delivery catheter (12) is passed through a lumen of the penetrator to the target site. A desired substance or apparatus is then delivered to or obtained from the target site.

WO 02/056937 A3



(15) Information about Correction:

Previous Correction:

see PCT Gazette No. 44/2002 of 31 October 2002, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/01168

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61M 31/00; A61M 5/178
 US CL : 604/500, 506-510, 164.01, 164.08-164.11, 164.13, 96.01, 99.02-99.04, 103.01, 103.06, 912, 915; 600/585, 433-435, 470; 606/167, 170, 181, 182, 184, 185

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Continuation Sheet

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,E	US 2002/0052576 A1 (MASSENGALE) 02 May 2002 (02.05.2002), entire document.	1,2, 13-21, 61, 69, 71, 76-80, 126, 127, 129, 130, 132, 135, 136, 138, 139, 141, 155, 156, 158-161, 164, 202 and 223
Y,E		3-12, 22-60, 62-68, 70, 72-75, 81-125, 128, 131, 133, 134, 137, 140, 142-154, 157, 162, 163, 165-201, 203-222 and 224-231



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"B" earlier application or patent published on or after the international filing date

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"O" document referring to an oral disclosure, use, exhibition or other means

"&"

document member of the same patent family

"P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

19 August 2002 (19.08.2002)

Date of mailing of the international search report

16 DEC 2002

Name and mailing address of the ISA/US

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 Washington, D.C. 20231

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Authorized officer

Gregory Huson

Telephone No. (703) 308-1113

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,366,490 A (EDWARDS et al.) 22 November 1994 (22.11.1994), entire document.	1-7, 126, 131, 138, 139 and 141-147
— Y		35-60, 128, 164, 169-201, 219 and 220
X,P	US 6,190,353 B1 (MAKOWER et al.) 20 February 2001 (20.02.2001), entire document.	1-7, 126, 131, 138, 139 and 141-147
— Y,P		35-60, 128, 164, 169-201, 219 and 220
X	US 5,762,630 A (BLEY et al.) 09 June 1998 (09.06.1998), entire document.	1, 61, 126, 132, 138, 139, 141, 202 and 223
— Y		22, 35-37, 44-46, 48-60, 128, 134, 148, 164, 175-177, 184-201 and 219-222
Y	US 5,533,516 A (SAHATJIAN) 09 July 1996 (09.07.1996), entire document.	8-10, 72, 73, 136, 149 and 150

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Species I as depicted in Fig. 3a

Species II as depicted in Fig. 4

Subspecies IIa as recited in claims 24-26, 102-104, 129, 135 and 164-166

Subspecies IIb as recited in claims 24, 27, 28, 102, 105, 106, 129, 135, 164, 167 and 168

Subspecies IIc as recited in claims 24, 29-34, 102, 107-115, 129, 135, 164 and 169-174

Species III as depicted in Fig. 5

Species IV as depicted in Figs. 6a, 6b

Species V as depicted in Fig. 7

Species VI as depicted in Figs. 8a, 8b

Species VII as depicted in Figs. 9a, 9b

Species VIII as depicted in Fig. 14

Species IX as depicted in Fig. 15

Species X as depicted in Fig. 16

Species XI as depicted in Fig. 17

The claims are deemed to correspond to the species listed above in the following manner:

Species I:	claims 127, 129, 133
Species II:	claims 24-34, 102-115, 129, 135, 164-174
Species III:	claims 8, 11-14, 71, 74-76, 130, 148, 151-154
Species IV:	claims 13, 15-17, 76-78, 130, 136, 153, 155-157
Species V:	claims 8-10, 71-73, 130, 136, 148-150
Species VI:	claims 19-21, 80, 130, 159-161
Species VII:	claims 19, 80, 130, 159
Species VIII:	claims 139, 141
Species IX:	claims 203, 205-218, 230, 231
Species X:	claims 201, 203, 204-218, 230, 231
Species XI:	claim 140

The following claim(s) are generic: 1-7, 18, 22, 23, 35-70, 79, 81-101, 116-126, 128, 131, 132, 134, 137, 138, 142-147, 158, 175-200, 202, 219-229.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

Each of the disclosed species has a patentably distinct feature from one another and a unique, special structure specified for its intended purpose.

INTERNATIONAL SEARCH REPORT

PCT/US02/01168

Continuation of B. FIELDS SEARCHED Item 1:

604/500, 506-510, 164.01, 164.08-164.11, 164.13, 96.01, 99.02-99.04, 103.01, 103.06, 912, 915; 600/585, 433-435, 470; 606/167, 170, 181, 182, 184, 185

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/01168

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

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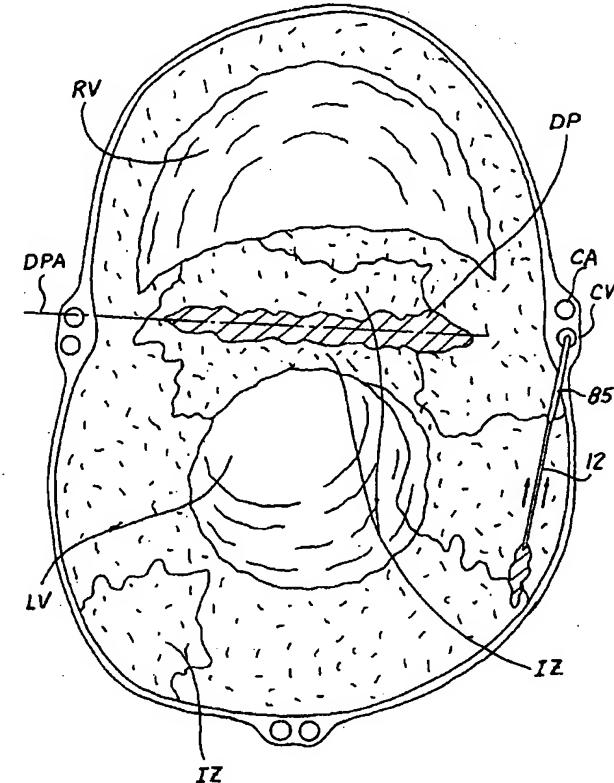
(72) Inventors; and

(75) Inventors/Applicants (for US only): **MAKOWER,**Joshua [US/US]; 450 Tyndall Street, Los Altos, CA 94022 (US). **LAMSON, Theodore, C. [US/US]**; 2172 Camino Brazos, Pleasanton, CA 94566 (US). **FLAHERTY, J., Christopher [US/US]**; 242 Ipswich Road, Topsfield, MA 01983 (US). **REGGIE, John, A. [US/US]**; 1145 Amarillo Ave. #15, Palo Alto, CA 94303 (US). **CHANG, John, Y. [US/US]**; 13080 Lorene Court, Mountain View, CA 94040 (US). **CANTANESE, III., Joseph [US/US]**; 1963 Woodwide Road # 9, Redwood City, CA 94061 (US). **THOLFSEN, David, R. [US/US]**; 263 Crescent Ave, San Francisco, CA 94110 (US).(74) Agent: **BUYAN, Robert, D.,** Stout, Uxa, Buyan & Mullins LLP, 4 Venture, Suite 300, Irvine, CA 92618 (US).

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(57) **Abstract:** Methods and apparatus for delivery of substances or apparatus to target sites located outside blood vessels within the body of a human or animal patient. A vessel wall penetrating catheter is inserted into the vasculature, positioned and oriented within a blood vessel near the target extravascular site and a penetrator is advanced from the catheter so as to penetrate outwardly through the wall of the blood vessel in the direction of the target site. Thereafter, a delivery catheter is passed through a lumen of the penetrator to the target site. A desired substance or apparatus is then delivered to or obtained from the target site. In some applications, the penetrator may be retracted into the vessel wall penetrating catheter and the vessel wall penetrating catheter may be removed, leaving the delivery catheter in place for chronic or continuous delivery of substance(s) to and/or obtaining of information or samples from the target site. Alternatively, a delivery catheter having an occlusion member or balloon may be advanced into a vein or venule and the occlusion member or balloon may be used to occlude the lumen of the vein or venule during and after injection of a substance through the catheter, such that the substance will not be carried away by normal venous blood flow and will remain in the vein or venule for a sufficient period of time to have its intended effect (e.g. to enter adjacent tissues through capillary beds drained by that vein or venule).



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**DEVICES, SYSTEMS AND METHODS FOR ACUTE OR CHRONIC DELIVERY
OF SUBSTANCES OR APPARATUS TO EXTRAVASCULAR TREATMENT
SITES**

5

Background of the Invention

There exist many situations in which it is desirable to deliver substances (e.g., drugs, biological materials, etc) or apparatus (e.g., wires, sensors, etc.) to specific locations within tissues (i.e. an "interstitial target site") of the body of a human or veterinary patient. Examples of the types of tissues wherein such target 10 sites may be located include myocardial tissue, brain tissue or tumors.

Some catheters and drug delivery stents of the prior art have been purportedly useable to *indirectly* deliver drugs or substances to specific interstitial target locations by first dispensing the drug *within* the lumen of a nearby blood vessel or on the inner surface of a nearby blood vessel and then allowing the drug 15 to migrate through the blood vessel wall or through a downstream capillary bed, to the desired interstitial target location.

The prior art has also included catheter devices that may be used for delivering substances or apparatus *directly* into interstitial target locations by guided advancement of a penetrating cannula or needle from a catheter located within the 20 lumen of a nearby blood vessel, through the wall of the blood vessel and through any intervening tissue, to the interstitial target site. The desired substance or apparatus may then be infused or delivered directly into the target interstitial site without any need for transmural diffusion through the blood vessel wall or downstream transluminal flow to the selected capillary bed. Examples of these 25 catheter devices useable for direct delivery of drugs or apparatus into interstitial target sites are described in PCT International Patent Publications No. PCT/US99/07115 and PCT/US99/07112.

Particular interest has developed in methods for controlled or targeted 30 delivery of substances such as drugs (e.g., chemotherapeutic agents), gene therapy compositions (e.g., plasmids, viral vectors, genetically modified cells, naked DNA), biological factors (e.g., angiogenic factors, nerve growth factors, other cell growth factors, other proteins), monoclonal antibodies, or specific cell types (e.g., stem cells or other progenitor cells, pancreatic islet cells, dopamine secreting

neurons, endothelial cells, myocardial cells, other myocytes, etc) into interstitial target locations for the purpose of treating diseases such as myocardial ischemia, solid tumor types of cancer, parkansonism, diabetes, etc. Specifically, in the treatment of myocardial ischemia, research has indicated that introduction of 5 certain angiogenic substances into ischemic areas of myocardium may result in "therapeutic angiogenesis" in patients who suffer from clinically significant coronary artery disease. Generally speaking, the term "angiogenesis" refers to the creation of new capillaries and/or blood vessels within the parenchyma of an organ, within a tumor or within an area of tissue (e.g., myocardium). Angiogenesis is believed 10 to occur as a multistep process in which endothelial cells focally degrade and invade through their own basement membrane, migrate through interstitial stroma toward an angiogenic stimulus, proliferate proximal to the migrating tip, organize into blood vessels, and reattach to newly synthesized basement membrane. The term "therapeutic angiogenesis" involves the administration of angiogenic 15 substances or treatments to promote one or more steps in the angiogenesis process thereby providing for the creation of new blood flow in tissue that previously lacked sufficient blood flow.

Various approaches have heretofore been used for delivery of angiogenic substances into the myocardium. One approach is the use a tissue penetrating 20 device such as a laser to create penetration tracts or transmyocardial (TMR) channels which extend from either the epicardial (outer) surface or endocardial (inner) surface of the heart into the myocardium, and to then inject quantities of angiogenic substances into those TMR channels. Examples of this approach are described in United States Patent Nos. 5,925,012 (Murphy-Chutorian, et al.), 25 5,999,678 (Murphy-Chutorian, et al.) And 6,106,520 (Laufer, et al.)

There remains a need in the art for the development of new apparatus and 30 methods for delivering substances or apparatus to specific target sites within tissues, tumors or organs of the body with minimal trauma to the tissues and optimum control as to the precise location(s) at which the substances or apparatus are introduced.

Summary of the Invention

The present invention provides transluminal methods, devices and systems for delivering substances (e.g., drugs or other therapeutic or diagnostic agents) or articles (e.g., devices, apparatus, wires, sensors, thermistors, etc.) to interstitial sites within the body of a human or veterinary patient.

In accordance with one aspect of the invention, there is provided a system comprising a) a penetrating catheter that is positionable within the vasculature (e.g., a blood vessel, vascular sinus or chamber of the heart) of a human or animal patient and which has a penetrator advanceable from the catheter in the direction of an extravascular target site and b) a delivery catheter that is advanceable from the penetrator to the target site. As used herein, the term "vessel wall" shall mean not only the wall of a blood vessel (i.e., artery or vein) but also the endocardium surrounding a chamber of the heart or any other wall of an anatomical structure in which the penetrating catheter is positioned and through which the penetrator advances to reach its intended position within adjacent tissue. The Substance(s), article(s) or apparatus may then be delivered to the target site through the delivery catheter and/or samples of body fluid or other information may be obtained from the target site through the delivery catheter. In applications where it is desired to use the delivery catheter continuously or intermittently over an extended period of time (e.g., hours, days, weeks or months) the penetrator may be withdrawn into the vessel wall penetrating catheter and the vessel wall penetrating catheter may be removed, leaving just the delivery catheter in place (e.g., extending through the patients blood vessel(s), outwardly through the penetration formed in the blood vessel wall and to the target site.) Also, the substance or article(s) may be injected periodically or continuously as the delivery catheter is being advanced or retracted, so as to provide a continuous "trail" or series of deposition sites wherein the substance or article(s) is/are deposited.

In accordance with the invention, the use of a unicurvate or multicurvate penetrator (or a curved delivery catheter in combination with a straight, unicurvate or multicurvate penetrator) may serve to guide the delivery catheter on a path that is navigates around anatomical structures or avoid penetration into a cavity, organ

or anatomical structure that the operator does not wish for the delivery catheter to enter. In this regard, the delivery catheter may be guided such that it advances on a path that is generally tangential to the wall or edge or a chamber of the heart or other cavity or anatomical structure that the operator does not wish to enter or 5 penetrate. This ability to avoid penetration of a chamber, cavity or anatomical structure may allow a greater length of the delivery catheter to be advanced into the tissue than would have been otherwise possible. The advancement of a greater length of delivery catheter into the tissue may allow for deposition of a longer trail or a more lengthy series of depots of an injected material than would be possible 10 if the delivery catheter were to have been advanced in the direction of or non-tangentially to the chamber of the heart or other cavity or anatomical structure that the operator does not wish to enter or penetrate. Also, the ability to provide a lengthy trail or series of deposition sites may be advantageous in certain 15 applications of the invention. For example, the ability to deposit a tissue graft or cells (e.g., stem cells, myoblasts, etc.) in an elongate trail may allow for the cells to form an organized structure wherein the cells communicate with one another and/or form a connection between two spaced apart regions of an organ or tissue mass. In cases where angiogenic substances are being injected through the delivery catheter, the ability to lay down a trail of the angiogenic substance may permit the 20 operator to define a line or elongate region of new blood vessel growth. Also, advancement of a more lengthy segment of the delivery catheter into the tissue may provide for deeper injection of substances with less potential for bleedback or regurgitation through the interstitial tract created by advancement of the penetrator and/or delivery catheter. Also, this capability of the system allows for the 25 deposition of a series or network of elongate trails or tracts of a substance or article, or spaced apart interstitial deposits of a substance or article in a manner that allows the individual trails, tracts or deposits to form a network and to interact with one another in a desired manner.

The types of substances that may be delivered through the delivery catheter 30 include drugs (thrombolytics, platelet inhibitors, anti-restenotic agents, beta blockers, ion channel antagonists, positive or negative ionotropic agents, anti-arrhythmics, antibiotics, analgesics, chemotherapeutic agents, other anti-neoplastic

agents, etc.), natural or recombinant proteins (e.g., angiogenic proteins such as vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF) nerve cell growth factor (NGF) or hepatocyte growth factor (HGF)), cells or cellular preparations (e.g., stem cells, other progenitor cells, myocytes, myoblasts, pancreatic islet cells, dopamine secreting cells, etc), genes or gene therapy preparations (e.g., viral vectors containing genes for gene therapy applications, genetic material for electrophoretic transmission into cells, plasmids, viral vectors, genetically modified cells, naked DNA, etc.), contrast media or dyes for imaging, 5 radio-labeled diagnostic materials or drugs or other traceable substances, mixtures of any of the above, alone, in solution or in combination with any delivery substance or matrix (e.g., polymer matrices used to inhibit or slow distribution or dissemination of a substance away from its original injection site), dialysis solutions or micro-dialysis solutions, or any other type of substances that may be introduced 10 through the delivery catheter for any therapeutic, imaging, diagnostic or other purpose.

Further in accordance with the invention, the types of target tissues into which the delivery catheter of the above-described system may be placed include various organs (e.g., heart, brain, liver, pancreas), the walls of blood vessels (by 20 injection directly into the vessel wall or by injection into a periadventitial area outside of but close to the vessel so that the drug or substance will be distributed into the vessel wall), muscles (e.g., myocardium, skeletal muscle) or aberrant masses (e.g., tumors, cysts).

Still further in accordance with the invention, substances delivered through 25 the delivery catheter may be of increased viscosity to deter their egress from the target area, may be adherent to tissues in the target area so as to deter egress of the substance from the target area and/or may harden or form a mass in situ after injection into the target area, thereby deterring egress of the substance from the target area.

30 Still further in accordance with the invention, the outlet port(s) of the delivery catheter may be configured such that substances injected through the

delivery catheter will form high pressure jet sprays into the tissue surrounding the delivery catheter.

Still further in accordance with the invention, the vessel wall penetrator of the vessel wall penetrating catheter and/or the delivery catheter may be equipped with 5 backflow deterrent for limiting or preventing fluid that is injected through the delivery catheter from bleeding back through the tissue tract through which the delivery catheter and/or penetrator was/were advanced. In chronic dosing applications wherein the delivery catheter remains indwelling, such backflow deterrent may comprise a balloon, annular rib or other barrier formed on the outer surface of the 10 delivery catheter to block the backflow of fluid through the tract in which the delivery catheter resides. In acute dosing applications wherein the delivery catheter is extracted and removed immediately after injection of the substance, the backflow deterrent may comprise a) an embolizing member such as a detachable blocker, balloon, clot, fibrin, bead of polyvinyl alcohol, etc. that is deployed into the tissue 15 tract as the delivery catheter and/or penetrator is/are retracted, b) a substance such as a cyanoacrylate, polyethylene glycol, hydrogel, fibrin glue or other material is injected to embolize, seal or close the tract through which the delivery catheter and/or penetrator was/were advanced or c) a tissue fusing device, such as a radio-frequency emitting electrode, for welding or fusing adjacent tissue in a way that 20 effectively closes the tract through which the delivery catheter and/or penetrator was/were advanced.

Still further in accordance with the invention, the delivery catheter of the 25 above-described system may be used for aspiration of samples of blood or body fluid from the target site and/or may include one or more interactive members, such as emitters, detectors, electrodes, sensors, etc. for a) facilitating the delivery catheter's penetration through tissue, b) facilitating the distribution of an injected substance into surrounding tissues (e.g., by iontophoresis), c) creating a pocket into which a substance may be injected or d) sensing the position of the delivery catheter or some content or variable (e.g., ECG, contractility, force of contraction, 30 pressure, local ECG amplitude, local protein levels, local antibody levels, pO₂, pCO₂, oxygen saturation, blood flow rate, pH, local lactate levels, etc.) of the adjacent tissue.

Still further in accordance with the invention, the delivery catheter may be used to continuously or intermittently monitor physiological parameters or variables (e.g., rate of blood flow away from the site) or pharmacokinetic or biodistributive parameters or variables (e.g., the rate at which a substance will distribute away from the target site, how long the injected substance may be expected to remain at the target site, the rate at which the injected substance may be inactivated or metabolized at the target site and/or other parameters/variables relating to the activity of the substance after it has been injected at the site). Such information may then be used to verify that the delivery catheter is suitably placed for optimal or desired therapeutic effect of an injected substance or apparatus delivered to the site. If it is determined that an injected substance is likely to distribute away from the target site too quickly, or remain at the target site for too long, or become inactivated too quickly or not quickly enough, the delivery catheter may be repositioned to a site that is more desirable. Similarly, if it is determined that the site is too vascularized or not vascularized enough for the desired therapeutic or diagnostic activity of the delivered substance or apparatus, the delivery catheter may be repositioned to a new target site that is suitably vascularized, before continuing with delivery of the substance or apparatus through the delivery catheter. One example of a manner in which this type of site monitoring may be accomplished is to deliver radio-opaque dye, a radio-labeled substance or other traceable material through the delivery catheter and to the location adjacent the outlet port(s) of the delivery catheter (i.e., the target site to which the therapeutic or diagnostic substance is being or will be delivered) Thereafter, the rate at which that traceable substance distributes away from that site (or the rate at which it becomes inactivated, degraded or metabolized) may be measured by appropriate means such as x-ray (when radio-opaque traceable material is used) or radio-scanning (when radio-labeled traceable material is used). If the site is deemed to be acceptable, the therapeutic or diagnostic substance or apparatus may be delivered to the site. If the site is deemed to be unacceptable (or less than optimal) the delivery catheter may be repositioned and the test may be repeated. In some applications, the delivery catheter may have multiple lumens such that a therapeutic or diagnostic substance or apparatus may be delivered through one lumen and a

traceable substance useable for site monitoring/verification may be delivered through another lumen.

Still further in accordance with the invention, the delivery catheter of the above-described system may include anti-obstruction apparatus (e.g., a mandrel, 5 stylet, inflatable member or semi-permeable barrier) that allows the desired substances or apparatus to be introduced in the distal direction through the delivery catheter but prevents cellular ingrowth or other matter from invading and obstructing the lumen and/or outlet port(s) of the delivery catheter. In this manner, the delivery catheter remains patent, even when it has been indwelling within tissue 10 for an extended period of weeks or months.

Still further in accordance with the invention, the efficacy of substances injected through the delivery catheter may in some applications be enhanced by limiting the rate at which the substance distributes away from the site or otherwise altering the biodistribution and/or pharmacokinetics of the substance after it has 15 been introduced into the body. This may be accomplished by introducing the substance in the form of a solid, dry pellet, implant, filament or gel. Alternatively, this may be accomplished by micro-encapsulating or mixing the substance with a polymer matrix, oil or other drug delivery matrix or material that is prepared before injection or formed in situ or by forming liposomes or colloidal suspensions 20 containing the substance, etc. Another way in which this may be achieved is by causing the substance to promptly enter cells rather than allowing the substance to remain disposed in intercellular fluids or intercellular spaces from which the substance may quickly distribute or disseminate away from the injection site (e.g., by driving the substance into adjacent cells by electrophoretic means or chemical 25 means, by modifying the properties (e.g., solubility, polarity, pH) of the substance in a manner which will facilitate its transport into cells, by atomizing or spraying the substance as it exits the catheter, or by causing the substance to exit the catheter at increased velocity or force.

The invention together with additional features and advantages thereof may 30 best be understood by reference to the following description taken in connection with the accompanying illustrated drawings.

Brief Description of the Drawings

Figure 1 is a schematic showing of a human patient who is undergoing a procedure for transvenous placement of a delivery cannula for ongoing delivery of drugs or apparatus to an ischemic region of the patient's myocardium.

5 Figure 2 is a broken, side view of one embodiment of a catheter system of the present invention.

Figure 2a is an enlarged, cut-away view of section 2a of Figure 2.

Figures 2b-2d show, in step-by-step fashion, the manner in which the 10 catheter system of Figure 2 may be used to accomplish transluminal placement of a delivery catheter for delivery of substances or apparatus to an extravascular target location.

Figure 3a shows an embodiment of a delivery catheter of the present invention which incorporates a subcutaneous injection port for periodic infusion of fluids through the delivery catheter.

15 Figure 3b shows an embodiment of a delivery catheter of the present invention which incorporates an exteriorized Luer fitting for attachment of a syringe to the delivery catheter for periodic infusion of fluids through the delivery catheter.

Figure 4 is a partial perspective view of a delivery catheter of the present invention having a plurality of side apertures for disseminated outflow of fluid 20 therefrom and a balloon for preventing injected fluid from backflowing through the tract through which the delivery catheter extends.

Figure 5 is a partial perspective view of a delivery catheter of the present invention having a plurality of side apertures for disseminated outflow of fluid therefrom and a stylet member that is insertable into the lumen of the delivery 25 catheter to block the side apertures at times when no fluid is being infused through the delivery catheter.

Figure 6a is a partial perspective view of a delivery catheter of the present invention having a plurality of side apertures for disseminated outflow of fluid therefrom and any inflatable obturator position within the lumen of the delivery 30 catheter in an inflated state wherein the obturator blocks the side apertures at times when no fluid is being infused through the delivery catheter.

Figure 6b is a partial perspective view of the delivery catheter of Figure 6 wherein the obturator is in a deflated state such that fluid may be infused through the lumen of the delivery catheter and out of the side apertures.

Figure 7 is a partial longitudinal sectional view of a delivery catheter the present invention having a plurality of side aperture is for disseminated outflow of fluid therefrom and a semi-permeable diffusion barrier mounted about the catheter such that fluid infused through the lumen of the delivery catheter and out of the side apertures will collect within the diffusion barrier and will subsequently diffuse outwardly through the barrier while the diffusion barrier prevents cellular matter or other material from invading and obstructing the side apertures or lumen of the delivery catheter.

Figure 8a is a partial longitudinal sectional view of a delivery catheter the present invention having an open distal end and a spring mounted tip member having a fluid outlet channel formed therein, such tip member being in a retracted position wherein the fluid outlet channel is fully covered by the catheter body and cellular matter or other material is prevented from invading and obstructing the fluid outlet channel.

Figure 8b is a partial longitudinal sectional view of the delivery catheter of Figure 8a, wherein fluid is being infused in the distal direction through the lumen of the delivery catheter and the pressure of the fluid has advanced the distal tip member to an extended position wherein the fluid outlet channel uncovered and fluid is permitted to flow from the lumen of the delivery catheter, outwardly through the fluid outlet channel.

Figure 9a is a partial perspective view of a delivery catheter the present invention having an open distal end and a coil spring mounted tip member mounted thereon, such tip member being in a retracted position wherein the convolutions of the coil spring are contracted into abutting contact with each other, thereby closing the lumen of the delivery catheter and preventing cellular matter or other material from invading and obstructing the lumen of the delivery catheter.

Figure 9b is a partial perspective view of the delivery catheter of Figure 9a wherein fluid is being infused in the distal direction through the lumen of the delivery catheter and the pressure of the fluid has advanced the distal tip member to an

extended position wherein the convolutions of the coil spring are spaced apart and fluid is permitted to flow from the lumen of the delivery catheter, outwardly through the spaces between the convolutions of the coil spring.

5 Figure 10 is a diagram of a human heart showing the manner in which a delivery catheter of the present invention may be transvenously implanted within an interstitial target site of the myocardium.

10 Figure 10a is an enlarged, cut-away view of a portion of Figure 10, showing the manner in which the delivery catheter extends through the wall of a coronary vein and in generally tangential relationship to the adjacent left ventricle of the heart.

15 Figure 11 is a diagram of a human heart showing the manner in which a delivery catheter of the present invention having a backflow preventing balloon thereon may be positioned within a coronary vein to deliver a substance to a target region of the myocardium by selective, retrograde infusion through the coronary vein.

20 Figure 12 is an enlarged, cut-away view of a portion of Figure 11, showing the backflow preventing balloon in an inflated state and a substance being infused through the delivery catheter and through the coronary vein in the retrograde direction.

25 Figure 13 is a partial, side view of a vessel wall penetrating catheter of the present invention showing the varying angles at which the vessel wall penetrating member may be deployed, relative to the longitudinal axis of the catheter body, depending on the extent to which the vessel wall penetrating member has been advanced.

30 Figure 14 is a partial perspective view of another tissue penetrating catheter system of the present invention.

Figure 15 is a diagram of the catheter system of Figure 14 positioned within a chamber of a human heart and being used to deliver a substance into the myocardial wall via an endocardial approach.

35 Figure 16 is a diagram of a modified catheter system of Figure 14 having a corkscrew penetrator positioned within a chamber of a human heart and being used to deliver a substance into the myocardial wall via an endocardial approach.

Figure 16a is a schematic diagram illustrating the manner in which the catheter system of Figure 16 may be used to deposit a series of radially arranged elongate tracts or trails of a substance within a mass of tissue creating a "wagon wheel" pattern of substance deposition within the tissue.

5 Figure 17 is a diagram of a catheter system comprising a tissue penetrating catheter having a laterally deployable penetrator combination with an optional guide catheter, positioned within a chamber of a human heart and being used to deliver a substance into the myocardial wall via an endocardial approach.

10 Figure 18 is a perspective view of a human heart having an area of necrotic myocardium due to a prior infarct, wherein a penetrating catheter of the present invention has been advanced into a coronary vein and the penetrator and delivery catheter are being used to deliver a therapeutic substance into the necrotic area of myocardium.

Figure 18a is an enlarged view of region 18a of Figure 18.

15 Figure 19 is a cross sectional view through line 19-19 of Figure 18.

Detailed Description of Preferred Embodiments

The following detailed description, and the drawings to which it refers, are provided for the purpose of describing and illustrating certain examples or 20 embodiments of the invention only and are not intended to exhaustively describe or show all possible embodiments or examples of the invention.

Generally, one method of the present invention may be carried out by first inserting a vessel wall penetrating catheter into the vasculature of a human or veterinary patient, advancing the vessel wall penetrating catheter through the 25 vasculature to a location within a blood vessel that is adjacent or near a target location at which a substance (e.g. a drug, biological or therapeutic agent) or apparatus (e.g. a sensor) is to be delivered and thereafter advancing a vessel wall penetrator from the catheter, transmurally through the wall of the blood vessel, in the direction of the target location. In some embodiments, the vessel wall penetrator itself may comprise a tubular member through which a substance or 30 apparatus may be passed. In those embodiments, the penetrator will be advanced all the way to the target location(s) and the substance or apparatus will then be

infused or delivered through the lumen of the penetrator. In other embodiments, a separate delivery catheter will be advanced through the vessel wall penetrator to the target location and, thereafter, the vessel wall penetrator may be withdrawn and removed (along with the entire vessel wall penetrating catheter) leaving only 5 the delivery catheter in place. This secondary catheter may then remain indwelling for whatever period of time is desired, to allow samples to be withdrawn from the target location or to allow therapeutic agents and/or apparatus (e.g. wires or sensors) to be introduced to the target location at desired intervals or on a desired schedule.

10 A. *Transluminally Deployable Catheter System for Acute or Chronic
Delivery of Substances or Apparatus to Interstitial Target Sites:*

15 Figures 2-2d show an example of a catheter system 10 of the present invention. This system 10 comprises the combination of a vessel wall penetrating catheter 11 and a delivery catheter 12. Figure 1 shows this catheter system 10 in use on a human patient.

Vessel Wall Penetrating Catheter

20 In the embodiment illustrated, the vessel wall penetrating catheter 11 includes an elongated catheter body 13 having a proximal end 15, a distal end 17, a handle 19 and a hub 21 coupled to the proximal end of the catheter body and to the handle. The handle 19 may also serve as a controller for use in advancing and 25 retracting the vessel wall penetrator 85, as described more fully below.

25 The vessel wall penetrating catheter body 13 includes a relatively rigid proximal section 23 shown in Figs. 2 and 3a which may be constructed, for example, of a metal hypo tube and an elongated flexible distal section or region 25 suitably joined to the proximal section. At least the distal section 25 is sized to be received within a coronary artery, and therefore can be received within either a coronary artery or a coronary vein. The catheter body section 13 has a penetrator lumen 27 which terminates distally at an exit location or exit port 29 that is located on a peripheral wall 31 of the catheter body. A vessel wall penetrator 85, such as 30 a hollow NiTi needle as shown in Figures 2a (phantom lines), 2b and 2c, is disposed within the penetrator lumen 27 and is advanceable out of the side exit port 29 as seen in Figures 2a-2c. The exit port 29 is preferably located a short distance

proximally of the distal end 17. A radiopaque marker 33 may be mounted on the lumen 27 adjacent the exit port 29 to facilitate placement and positioning of the vessel wall penetrating catheter 11. The penetrator 85 may be a single hollow member or may consist of a series of hollow members which advance through one another or telescope in a desired manner. In embodiments where the penetrator consists of a plurality of hollow members which advance through one another or telescope, the individual members may have differing curvatures or differing shapes to allow the penetrator or follow a multicurvate path of advancement. This may be useful in applications where the penetrator is required to advance around a prohibited zone or anatomical structure that the operator does not wish to penetrate.

The catheter body 13 also has a guidewire lumen 35 (Fig. 3a) which extends to the distal end 17 of the catheter body 15. In this embodiment, the guidewire lumen 35 extends proximally to an inlet port 37 at the peripheral wall 31 closely adjacent the proximal section 23.

A major section 51 of the catheter body 13 terminates distally in a distal opening 53, and the catheter body includes a distal tip section 55 of soft, flexible, biocompatible material (Figs. 3a and 3b). A proximal portion 56 of the distal tip section 55 is received in the distal opening 53 and a distal portion of the distal tip section 55 extends distally to the distal end 17. The distal portion of the distal tip section 55, i.e. the portion of the distal tip section 55 which extends beyond the distal end of the major section 51 is of smaller cross sectional area than the adjacent region of the major section to thereby define an annular shoulder 57 on the catheter body 13. The exit port 29 is spaced slightly proximally of the shoulder 57.

Guidance Elements

In many embodiments, it will be desirable for the vessel wall penetrating catheter 11 to include a guidance element for guiding the positioning and rotational orientation of the catheter 11 within the vasculature such that the vessel wall penetrator 85 will be properly aimed in the direction of the target site. Such guidance element may include marker(s), imaging apparatus, emitter(s), sensor(s)

etc. In the particular embodiment shown in figures 2a and 2b, the guidance element comprises the combination of an imaging transducer 81 and an imageable marker assembly 101. The imaging transducer 81 is fixedly mounted on the catheter 11, and in the embodiment illustrated in Fig. 3a, the imaging transducer 5 is mounted on the distal tip section 55 just distally of the shoulder 57. In this embodiment, the imaging transducer 81 is a phased array transducer and is operative to image 360° about the vessel wall catheter 11. The imaging transducer 81 is coupled to a multiplex circuit 83 which is within the major section 51 of the catheter body 13 adjacent the shoulder 57, and the multiplex circuit 83 is in turn 10 coupled to leads 85 which extend through the lead lumen 39, through the handpeice 19 and are attached to a connector 86 which allows the leads 39 to be connected to a viewing instrument and screen. When activated, the imaging transducer emits ultrasound signals and receives back echos or reflections which are representative of the nature of the surrounding environment. The imaging 15 transducer provides an imaging signal from which an image of the surrounding structure can be created on a screen of the viewing instrument. In a preferred practice of this invention, the phased array transducer, the accompanying circuitry and the separate viewing instrument/screen may be obtained from Endosonics, Inc. of Rancho Cordova, California.

20 In an alternate embodiment of this invention, the imaging element may be formed of a single rotating crystal or transducer. In this embodiment the transducer would have a single lead out, would include a drive shaft which would run back to the proximal end of the catheter through 39.

25 In the particular embodiment shown, an imageable marker 101 is fixedly mounted on the catheter body 13 in a known circumferential orientation relative to the exit port 29. This marker 101 may be in the form of a structure or cage, as shown, and the transducer 81 may be located within the marker cage or marker structure. In the embodiment shown, the marker cage comprises a plurality of longitudinal members 103 disposed at circumferentially spaced apart locations 30 about a hollow interior space 105. The hollow space 105 receives the distal tip section 55 and the transducer 81, and the transducer 81 is an onboard transducer in that it is inseparable from and not removable from the catheter body 13. One of

the longitudinal members is located at a circumferential position that is axially aligned with the exit port 29 and consequently is also axially aligned with the path that will be followed by a tissue penetrator that is advanced from the catheter body 13 through the exit port. Thus, the imageable marker 101 forms on the image 5 obtainable from the imaging signal from the imaging transducer a penetrator path indication that indicates the path that will be followed by the tissue penetrator when the tissue penetrator is advanced from the catheter. As an alternative to the use of a marker 101, the path that will be followed by the penetrator may be indicated on the image by electronic means or by the use of a computer program, thereby 10 eliminating the need for a penetrator path indicating marker 101. In many embodiments, the marker 101, electronic penetrator path indicator or computer program for determination of the penetrator path may not only indicate the trajectory or path of the penetrator but may also indicate a stopping point at which advancement of the penetrator will stop or is intended to stop. By providing such 15 an indication of the mandatory or intended stopping point of the penetrator advancement, the operator may cause the penetrator to be optimally positioned at the intended site without advancing the penetrator too far as may result in missing of the intended delivery site or unwanted penetration of a blood vessel or other anatomical structure that lies beyond the site at which the penetrator is desired to 20 stop.

With the construction described above, the imaging transducer 81 and the marker 101 are both mounted on the distal tip section 55 which has a smaller cross 25 sectional area than does the adjacent region of the major section 51 of the catheter body 13. Accordingly, the cross sectional area of the catheter body 13 at the region containing the imaging transducer 81 and the marker 101 can still be relatively small. Also, the exit location 29 is closely adjacent to the imaging transducer 81 and may be, for example, about 5 mm from the imaging transducer. This minimizes the likelihood of any significant torsional displacement of the exit location 29 relative to the marker 101 and imaging transducer 89. It may also be appreciated that the 30 imaging transducer may be mounted such that the exit port is located directly at the point at which the transducer is affixed to the catheter, illuminating any displacement.

It will be appreciated that various other types of imaging or position sensing apparatus may be used as alternatives to the above-described imaging transducer 89/marker 101 combination to guide and orient the vessel wall penetrating catheter 11. For example, the vessel wall penetrating catheter 11 may incorporate an 5 emitter that is useable in conjunction with an electromagnetic, potentiometric, or other electro-anatomical mapping and/or catheter guidance/positioning systems, such as those commercially available from or under development by Biosense Webster, Inc., Diamond Bar, California; Cardiac Pathways Corporation, 995 Benicia Avenue, Sunnyvale, CA and/or Stereotaxis, Inc., 4041 Forrest Park Avenue, St. 10 Louis, MO. Examples of these types of catheter guidance or positioning systems are described in United States Patent Nos. 5,820,568 (Willis), 5,931,818 (Werp et al.), 5,654,864 (Ritter et al.), 5,928,248 (Acker), 5,752,513 (Acker et al.), 5,558,091 (Acker et al.) And 5,833,608 (Acker), the entire disclosures of which are expressly incorporated herein by reference.

15 Delivery Catheter

After the vessel wall penetrator 85 has been advanced to the desired extended position, the delivery catheter 12 may be advanced through the lumen of the penetrator 85 and out of its distal end. For applications where it is desired for the delivery catheter 12 to penetrate into myocardial tissue, the delivery catheter 20 12 may comprise a small cannula, hypotube or microcatheter formed of a suitable material such as polyimid, polytetrafluoroethylene, polypropylene, polyethylene, Pebax™, etc. For many applications, including application wherein the delivery catheter-12 is used to deliver substances into the myocardium, the delivery catheter 12 may have an outer diameter of approximately 0.25-0.5 mm. In embodiments 25 where it is intended for the delivery catheter to penetrate through tissue as it advances the distal tip of the delivery catheter 12 may be beveled or sharpened. Optionally, the delivery catheter 12 may have an energy emitting distal tip for enhanced tissue penetrating capability. For example, a radiofrequency electrode may be located on or near the distal tip of the delivery catheter to provide for tissue 30 penetration enhanced by RF energy emission. Or, the delivery catheter may be adapted to ultrasonically vibrate, thereby improving its ability to penetrate through tissue.

The body of the delivery catheter 12 may be radio-opaque or one or more radio-opaque markers may be formed on the delivery catheter (e.g., at its distal tip) to permit imaging of the catheter and determination of the position of the catheter within the patient's body.

5 In some applications, such as those where drugs, substances or apparatus are to be chronically delivered to the target site over a period of days, weeks or months, the delivery catheter will be allowed to remain indwelling after the vessel wall penetrating catheter 11 has been removed. To facilitate this, a detachable or removable Luer connector 47 may be mountable proximal end of the delivery catheter
10 12 as shown in Figures 2 and 3b. This detachable or removable Luer connector may be removed when during proximal withdrawal and removal of the vessel penetrating catheter 11 while the delivery catheter 12 remains in place. Thereafter, in embodiments wherein the proximal end of the delivery catheter 12 remains exteriorized, the removable or detachable Luer connector 47 may be attached to
15 the exteriorized proximal end of the delivery catheter 12 and may thereafter be used for subsequent attachment of a stopcock 47 and/or syringe 50 as shown in Figure 3b. In other embodiments, the proximal end of the delivery catheter 12 may be devoid of any hub or connector and may be connected to a pump, delivery device, subcutaneously implanted reservoir or injection port 52, as shown in Figure
20 3a.

An opening for infusion or aspiration of substances/apparatus may be formed in the distal end of the delivery catheter 12 and/or one or more fluid outlet openings may be formed in the sidewall of the delivery catheter 12, near its distal end, as shown in figures 2c or 2d. For many applications, one or more openings
25 may be laser drilled into the delivery catheter 12, such openings being no more than $\frac{1}{2}$ the diameter of the catheter lumen through which the substance is being injected, such that high pressure jets of the substance will be created as the substance exits the delivery catheter 12. The creation of such elevated pressure as the substance exits the delivery catheter 12 serves to propel or drive the substance through cell membranes and into intracellular spaces cells rather than
30 allowing the substance to remain in intercellular spaces (i.e., spaces or fluids

between cells or outside of the cells) from which the substance would more rapidly distribute away from the injection site.

The delivery catheter may be straight or curved, as needed to accomplish the desired procedure. In some but not necessarily all cases, the delivery catheter 5 may constitute a very small diameter catheter of a type known in the art as a microcatheter.

Interactive Apparatus on Delivery Catheter

As shown in Figure 2c, one or more interactive members 52 such as sensors, emitters, etc. may be positioned on or near the distal end of the delivery catheter 12 for emitting energy as described above or for sensing, sampling or receiving information from the tissues adjacent the distal portion of the delivery catheter 12. Interactive members that comprise sensor(s) may provide information on the position of the delivery catheter 12 or measurements of variables such as ECG, contractility, force of contraction, pressure, local ECG amplitude, local protein 10 levels, local antibody levels, pO_2 , pCO_2 , oxygen saturation, blood flow rate, pH, local lactate levels, etc. By use of such information received from the target site, the clinician may assess or characterize the target site to ascertain its suitability 15 before introducing a substance or apparatus into the target site.

In applications where it is desired to facilitate the passage or distribution of 20 an injected substance into the surrounding tissue, the interactive member 52 may emit some facilitating energy, such as an electromagnetic field for iontophoretic transmission of the substance through the adjacent tissue.

—In other applications, the interactive member 52 may emit energy, such as 25 radiofrequency energy, that will create a pocket in the surrounding tissue such that a substance or apparatus may be introduced into that pocket. The walls of the pocket may be seared by the energy so as to slow the distribution of the substance out of the pocket.

In other applications, the interactive member 52 may emit energy, such as 30 ultrasound, that facilitates distribution of a substance by permeating cell membranes or by vibrating the catheter tip.

Apertures for High Pressure Injection from Delivery Catheter

As shown in Figures 2c and 2d, the distal end of the delivery catheter may be closed and a plurality of small side apertures 24 may be formed in the sidewall 5 of the delivery catheter 12 to provide for high pressure outflow of fluid from the delivery catheter and into the surrounding tissues.

Backflow Deterrent Apparatus on Delivery Catheter and/or Penetrator

In some applications, the injection of fluids through the delivery catheter 12 into a closely confined space or interstitial site may result in some regurgitation or 10 backflow of the injected fluid through the tract through which the vessel wall penetrator 85 and/or delivery catheter 12 were advanced. In acute dosing situations where the delivery catheter is removed immediately after the dose, this 15 backflow of the injected fluid may be prevented by sealing the penetration tract or by introducing a material (e.g., an adhesive or embolizing material) into the tract during immediately after removal of the catheter 12. This may be accomplished by injecting a suitable adhesive or embolizing material such as a cyanoacrylate, polyethylene glycol, hydrogel, fibrin glue through the delivery catheter lumen as the delivery catheter 12 is being pulled back through the tissue tract through which it was initially inserted. In other applications where the delivery catheter 12 remains 20 indwelling, the backflow of fluid may be accomplished by a backflow barrier 22 (see Figure 4) such as an annular rib or inflatable balloon formed on the shaft of the delivery catheter 12 near its distal end so as to block backflow of fluid around the catheter shaft or alternatively by causing the fluid to solidify or become gelatinous such that it can not backflow through the penetration tract. Such gelling or 25 solidification of the injected fluid may be accomplished by subsequent injection or pre-mixing of the fluid with an oil, a gelatinous polymer carrier or reactant that will cause the desired thickening or solidification of the injected fluid.

Anti-Obstruction Apparatus for Maintaining Patency of Delivery Catheter

In some embodiments, especially those in which the delivery catheter 12 is 30 allowed to remain indwelling for chronic delivery of substances or apparatus to the target site, the delivery catheter may incorporate anti-obstruction apparatus that will prevent cellular ingrowth or other matter from obstructing the lumen or outflow

port(s) of the delivery catheter 12. Examples of such anti-blocking apparatus are shown in Figures 5-7.

In the embodiment of Figure 5, the delivery catheter has a closed distal end 28 and a plurality of side outlet apertures 24. A solid stylet 26 is insertable through the lumen of the delivery catheter and the outer diameter of the stylet 26 is approximately the same as the inner diameter of the delivery catheter such that, when inserted, the stylet 26 will substantially close-off or block the side apertures 24 thereby preventing cellular ingrowth or other matter from entering the side apertures 24 or lumen of the delivery catheter. Thus, the stylet 26 may be inserted into the delivery catheter at times when no fluids or other substances are being infused, but may be removed at appropriate times to allow the desired infusions of fluids or other substances through the delivery catheter.

In an alternative variation of the embodiment shown in Figure 5, the stylet 26 could have a lumen which extends longitudinally through the stylet to a closed distal end and side aperture(s) or slot(s) or other opening(s) could be formed in the stylet so as to be alignable with the side apertures 24 of the delivery catheter. In such embodiment, the stylet would be maintained in one position when it is desired to block the side apertures 24 to prevent cellular ingrowth or other matter from entering the side aperture's or lumen of the delivery catheter but may be rotated or otherwise moved to a second position wherein the aperture(s), slot(s) or other opening(s) of the stylet 26 would become aligned with the side aperture's 24 of the delivery catheter such that fluid may be injected through the lumen of the stylet and outwardly through the side apertures of the delivery catheter 24. Thereafter, when the fluid injection has been completed, the stylet could be once again rotated or otherwise moved to the first position to once again close-off or block the side apertures 24 of the delivery catheter.

Figures 6a and 6b show another embodiment wherein the delivery catheter has a closed distal end 28 and a plurality of side outlet apertures 24. In this embodiment, an inflatable obturator 30 is disposed within the lumen of the delivery catheter. When the obturator 30 is inflated, as shown in Figure 6a, it will close-off or block the side apertures 24 thereby preventing cellular ingrowth or other matter from entering the side apertures 24 or lumen of the delivery catheter. However,

when the obturator 30 is deflated, as shown in Figure 6b, fluids may be infused in the distal direction through the lumen of the delivery catheter and out of the side apertures 24.

In the embodiment of Figure 7, a semi-permeable diffusion barrier 58 is 5 mounted about the outer surface of the delivery catheter so as to cover the catheter's side apertures 24. This diffusion barrier 58 is in the nature of a balloon and is formed of material that permits the substances or fluids injected through the catheter to diffuse outwardly through the barrier 58, but also prevents cellular ingrowth or other matter from invading the interior of the barrier 58 and entering the 10 side apertures 24 or lumen of the delivery catheter. The desired semi-permeability of the diffusion barrier 58 may be a function of the size of pores or openings in the barrier or balloon 24. Thus, polymer films having appropriately sized pores may be used to form the diffusion barrier 58. One polymer material that may be used in film form to create the diffusion barrier 58 is commercially available as Nutrapore™ from 15 Anamed, Inc., 1 Technology Drive, Bldg. D-409, Irvine, CA 92618.

Figures 8a and 8b show another embodiment of a delivery catheter 12 having it opened distal end and a spring-mounted tip member 42 disposed within the distal end of the catheter 12. The tip member 42 has a fluid flow channel 44 that extends through the tip member 42 and opens through the side of the tip 20 member 42, as shown. The tip member 42 is attached to the catheter 12 by way of a spring 40. The spring 40 is biased to a contracted position as shown in Figure 8a, wherein the tip member 42 is drawn into the lumen of the catheter 12 such that the side opening of the fluid flow channel 44 is covered by the wall of the catheter 12 and cellular ingrowth or other matter is thereby prevented from entering the fluid 25 flow channel 44 or lumen 32 of the delivery catheter 12. However, as shown in Figure 8b, when fluid or some substances injected in the distal direction through the lumen 32 of the catheter 12, the pressure of the fluid or other substance will overcome the bias of the spring 40, causing the tip member 42 to advance to a second position whereby the side opening of the fluid flow channel 44 becomes 30 unobstructed and the injected substance or fluid is permitted to flow outwardly through the fluid flow channel 44 and out of its side opening, into the surrounding tissue. Thereafter, when the substance or fluid is no longer being injected, the bias

of the spring 40 will cause the tip member 42 to retract to its first position as shown in Figure 8a.

In the embodiment shown in Figures 9a and 9b, there is provided a delivery catheter 12 that has an open distal end, a generally conical tip member 408 and a coil spring member 46 which attaches the tip member 48 to the distal end of the catheter 12. The coil spring member 46 is biased to a retracted position, as shown in Figure 9a, wherein the convolutions of the coil spring member 46 are drawn into abutment with one another and with the respective ends of the catheter body 12 and tip member 48. In this manner the distal end of the catheter 12 is substantially closed, and cellular ingrowth or other matter is prevented from invading the lumen of the catheter 12. However, as shown in Figure 9b, when a fluid or substance is injected through the lumen of the catheter 12 the pressure of the injected fluid or substance will overcome the bias of the coil spring member 46, thereby causing the tip member 46 to advance in the distal direction and the convolutions of the coil spring member 46 to separate such that spaces 46a will exist between the individual convolutions of the coil spring member 46. The injected substance or fluid will thus flow outwardly through the spaces 46a and into the surrounding tissue. After the injection of the substance or fluid has stopped, the bias of the coil spring member 46 will cause the tip member 48 to become retracted and the device will assume its closed configuration as shown in Figure 9a.

Another way in which the patency of the lumen of the delivery catheter 12 may be maintained is by constant infusion and withdrawal of fluid therethrough. In this regard, fluid may be continually or periodically infused into a tissue pocket or reservoir at the distal end of the delivery catheter 12 and subsequently re-aspirated through the delivery catheter lumen. Alternatively, the delivery catheter 12 may have multiple lumens, one for infusion of fluid and one for withdrawal of fluid, and a periodic or continual infusion and withdrawal of fluid may be performed to keep these lumens of the delivery catheter 12 open and unobstructed with cellular ingrowth, clots, debris or other matter.

30 Apparatus/Substances for Anchoring of Delivery Catheter

The delivery catheter 12 may incorporate mechanical hooks, screws, barbs or other anchoring members (not shown) that engage surrounding tissue and deter

inadvertent migration or movement of the delivery catheter 12 after it has been implanted. Such anchoring members may be formed of bioabsorbable material and may be designed to break away, detach upon delivery of a pulse of energy or to be otherwise jettisoned when the delivery catheter 12 is purposefully removed from the body. In instances where the optional interactive member 52 comprises an energy emitter or electrode, such as a radiofrequency electrode, such interactive member 52 may be actuated after the delivery catheter 12 is in place for the purpose of fusing the catheter 12 to the surrounding tissue. Also, chemical glues, adhesives, or an ingrowth matrix such as a fabric (e.g., a woven material such as Dacron) into which surrounding tissue will grow, may be disposed on the delivery catheter 12 or introduced through the delivery catheter 12 after it is positioned, to deter inadvertent movement of the delivery catheter 12.

Other Surface Treatments of the Delivery Catheter

Apart from the above-described disposition of glues, adhesives or an ingrowth matrix on the surface of the delivery catheter 12 to facilitate its anchoring, there may additionally be other types of surface materials or surface treatments applied to the delivery catheter 12 for various other reasons. For example, the outer surface of at least the portion of the delivery catheter that becomes inserted into the patient's body may be coated or impregnated with an antibiotic or antimicrobial substance (e.g. provodine iodine, silver compounds, etc.) or other drugs or substances that affect the surrounding tissue in a desired way (e.g., a heparin coating that will reduce clot formation in areas adjacent to the catheter or within the blood vessels through which the catheter extends). One example of an anti-microbial coating that may be applied to the delivery catheter 12 is a proprietary material containing silver, carbon and platinum and used commercially under the name Oligon™ (Edwards Lifesciences Corporation, Irvine, California). Examples of commercially available heparin coatings that may be used include heparin-benzalkonium chloride complex, heparin-TDMAC complex and other medical coatings available from STS Biopolymers, Inc. 336 Summit Point Dr., Henrietta, NY.

Apparatus for Creating Pocket into Which Substance or Apparatus is Introduced:

The delivery catheter 12 may optionally incorporate, or may be used in conjunction with, apparatus for creating a pocket (e.g., a void) within tissue located adjacent to the outflow aperture(s) 24 of the delivery catheter 12 such that substances infused through or apparatus introduced through the delivery catheter 12 will be received within that pocket. For example, an expandable cage may be deployable through or from the delivery catheter 12 to spread or separate the adjacent tissue, thereby creating the desired pocket. Or, the above-described interactive member 52 may comprise an energy emitting apparatus capable of creating a pocket adjacent thereto. In this regard, the interactive member 52 may comprise a radiofrequency electrode that, when actuated, will ablate the adjacent tissue thereby creating the desired pocket. Alternatively, the pocket creating apparatus may comprise a laser port through which ablative laser energy may pass into the adjacent tissue, or a nozzle through which a high pressure jet of fluid may be injected so as to sever or separate the adjacent tissue, thereby creating the pocket.

Variable Delivery Catheter Trajectory from Single Penetrator

Figure 13 shows that the vessel wall penetrator 85 may be of a pre-bent, curved configuration such that incremental advancement of the penetrator may cause its distal tip to be incrementally positioned at a series of different locates, such as point A (PA), point B (PB), point C (PC) and point D (PD) shown in Figure 13. The delivery catheter 12 may then be advanced out of the penetrator at each of the points and drug or substances may be injected at periodic depot locations DL along the path of each advancement or retraction of the delivery catheter 12. In this manner, the drug or other substance may be deposited relatively uniformly over a generally wedge shaped region of tissue with only one penetration through the vessel wall.

B. Procedure for Transluminal Placement of a Delivery Catheter Within and Interstitial Target Site and Acute or Chronic Delivery of Substances or Apparatus to The Target Site:

Figure 1 generally depicts a catheter system 10 of the above-described type being used to perform a procedure for transvenous placement of a delivery catheter 12 in an ischemic region of the patient's myocardium (i.e., the target site) so that a substance or apparatus may be acutely or chronically delivered directly into the target site.

This procedure begins with the percutaneous insertion of the vessel wall penetrating catheter 11 into the patient's femoral vein and advancement of the vessel wall penetrating catheter 11 through the inferior vena cava, through the right atrium, through the coronary venous sinus and into a coronary vein as shown in detail in Figure 11. A vessel wall penetrator 85 is then advanced from the vessel wall penetrating catheter 11 and through the wall of the coronary vein in which the vessel wall penetrating catheter 11 is positioned. Thereafter, a delivery catheter 12 is advanced through the vessel wall penetrator 85 to the target location within the patient's myocardium.

In many applications, the vessel wall penetrating catheter 11 will be provided with or associated with guidance elements as described hereabove to guide the positioning, rotational orientation of the catheter 11 within the patient's body and/or the path, trajectory and extent of advancement of the penetrator 85. Typically, these guidance elements will be used to guide the longitudinal position and rotational orientation of the vessel wall penetrating catheter 11 before the penetrator 85 is advanced from the catheter 11. Thereafter, after the delivery catheter 12 has been advanced through the penetrator 85 to the target site, the penetrator 85 may be retracted into the vessel wall penetrating catheter 11 and the vessel wall penetrating catheter 11 may be withdrawn and removed, leaving only the delivery catheter 12 in place.

Optionally, as shown in Figure 2c, an interactive member 52 such as an emitter, sensor, marker, electrode, etc. may be mounted on the delivery catheter 12. This interactive member 52 may be sensor (e.g., an electrode, optical sensor, chemical sensor, strain gage, flow meter, etc) that is connected to a receiver or instrumentation located outside the patient's body so as to provide information or analytical data regarding from the target site TS. Examples of the types of information or data that may be sensed and provided from the target site include

ECG, contractility, force of contraction, pressure, local ECG amplitude, local protein levels, local antibody levels, pO_2 , pCO_2 , oxygen saturation, blood flow rate, pH, local lactate levels, etc.

Substances or apparatus may be introduced through the lumen of the 5 delivery catheter 12 at desired time points or intervals. Also, separate sensor(s) or other separate apparatus may be delivered through the delivery catheter 12 so as to provide diagnostic information or other information regarding the physiological status of the myocardium in which the delivery catheter 12 is indwelling and/or the specific positioning of the distal end of the second catheter 12. After all of the 10 desired sampling, diagnosis, delivery of substances and/or delivery of apparatus has been completed, the dosing catheter 12 may then be removed from the body of the patient. Some examples of tissue penetrating catheters 10 useable in this invention include those described in PCT International Patent Publications No. PCT/US99/07115 and PCT/US99/07112.

15 The delivery catheter 12 may comprise any suitable type of flexible catheter sized to pass through the lumen of the vessel wall penetrator 85 in the manner described here above. Examples of commercially available extrusion that may be used to form the delivery catheter 12 include a

20 When the invention is used to deliver substances (e.g., drugs, therapeutic agents, biologicals, etc.) to ischemic site(s) within the myocardium, the types of substances that may be delivered include angiogenic factors (e.g. VEGF, FGF, EGF, PDGF or Hepatocyte Growth Factor ("HGF")), gene therapy compositions (e.g. a replication-deficient adenovirus vector containing a transgene which codes for an angiogenic protein or peptide), pro-angiogenic agents or combinations (e.g. 25 an adenosine receptor agonist in combination with heparin), myocardial cells, myocytes, myoblasts, or other cardiac or systemic drugs such as antiarrhythmic agents, beta blockers, calcium channel antagonists, platelet glycoprotein (GP) IIb/IIIa inhibitors, etc.

30 In some applications, the invention may be used to treat neurodegenerative diseases such as Parkinson's Disease, Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease), Alzheimer's Disease, etc.) By delivering to a target site within the brain or central nervous system a substance that delays the nerve cell degeneration or

causes new nerve cells or new nerve cell connections to form, such substances including but not limited to glial cell line-derived neurotropic factor (GDNF), nerve growth factor, neuro-immunophilin ligand, poly ADP-Ribose polymerase, and combinations thereof.

5 In some applications of the invention, the delivery catheter 12 will be provided with small side apertures 24 and a closed distal end, or some other aperture or nozzle arrangement, that causes the substance to be expelled from the delivery catheter 12 in fine, high velocity jets or streams such that dissemination of the substance into the surrounding tissue will be enhanced. In some instances an
10 10 interactive member 52 on the delivery catheter may be used emit energy or otherwise interact with the delivered substance to affect the substance in a desired way (e.g., to emit an iontophoretic field to drive the substance into adjacent tissue or to cause the distal tip of the delivery catheter 11 to become warm or to vibrate ultrasonically in a way that enhances the distribution or cell membrane permeation
15 15 of the substance). Also, in some applications, a substance injected through the delivery catheter 12 may be mixed with or followed by a second substance which causes the first substance to solidify, gel, adhere or to become otherwise altered in a desired manner (e.g., in a way that affects the distribution, bioavailability, potency, duration of action or pharmacologic activity of the first substance. In this
20 20 regard, a mixture of angiogenic factors (e.g., VegF and FGF) may be prepared in a liquid polymer matrix and injected in a bolus through the delivery catheter 12 into a myocardial target site. Thereafter, a second solution containing a catalyst that causes the polymer matrix to solidify to form a biodegradable solid may be injected as a second bolus through the delivery catheter. The mixture of the first solution
25 25 with the second solution within the target site will cause the first solution to solidify in the form of a biodegradable solid or foam. This in situ solidification of the matrix will cause the injected angiogenic factors to remain within the target site for a longer period of time than if they had been injected and allowed to remain as an aqueous solution. Examples of materials that may be formed in situ in this application
30 30 include those described in United States Patent No. 6,139,574 (Vacanti).

The present invention allows for mapping or assessment of the site at which the delivery catheter 12 is positioned to confirm that the site is, or continues to be,

suitable for the intended purpose. For example, a radio-labeled compound, radio-isotope or other traceable substance may be introduced through the delivery catheter and the rate at which the radio-labeled substance or isotope distributes away from the injection site may be measured by well known techniques. If the 5 distribution away from the site is determined to be too rapid or too slow, the delivery catheter 12 may be repositioned before the desired therapeutic or diagnostic substance is injected. In chronic dosing applications wherein the delivery catheter 12 remains indwelling for days or months, this technique may be used to ensure that the delivery catheter 12 has not migrated or moved from the intended injection 10 site, or that the site has not become excessively vascularized since delivery of the last dose. In some applications, it may be desirable for the delivery catheter 12 to have multiple lumens, such that the desired therapeutic or diagnostic substance or apparatus may be delivered through one lumen and a traceable substance useable for mapping or assessment of the target site may be delivered through another 15 lumen.

It will be appreciated that the above-described examples of the application of the catheter system 10 may further be combined with some or all of the other optional elements of the catheter system 10 described here above, such as the high-pressure distribution nozzles, tissue-pocket-creating apparatus, sponges or 20 other apparatus/substances afford to wait or affect the dissemination or distribution of the injected substance, anti-obstruction apparatus, apparatus/substances for a three of the delivery catheter, sensors or other apparatus for characterization of the targets i.e. or regions adjacent the delivery catheter, etc.

C. Method for Intravenous Retroperfusion

25 The present invention further includes a method wherein a retrovenous delivery catheter 112, as shown in Figures 11 and 12, is used to deliver a substance into a vein while temporarily obstructing the vein, thereby allowing the substance to enter a target site by undergoing retrograde flow through the venous vasculature to a capillary bed at the target site. The retrovenous delivery catheter 112 generally comprises a flexible tubular catheter described hereabove of the above- 30 described type may be inserted into a selected vein (e.g., a coronary vein) and used acutely or chronically to deliver substances to a particular target site by

retroperfusion of the substance through the vein, to a capillary bed located within the target site. An example of this embodiment of the invention is shown in Figures 11 and 12. As shown, the retrovenous catheter 112 has a distal end opening and an inflatable occlusion balloon 50 formed a spaced distance proximal to the distal 5 end opening. The catheter 112 is inserted into the venous vasculature and advanced into a specific vein such as a coronary vein located near an area of ischemic myocardium, as shown in Figures 11 and 12. Before a desired substance is delivered through the catheter 112, the occlusion balloon 50 is inflated so as to 10 occlude the vein and prevent venous blood from flowing through the vein in the normal direction of venous blood flow. The desired substance (e.g., a drug or biological) is then injected through the catheter 112 and out of its distal end opening 15 into the vein. Because the vein is occluded by the balloon, the injected substance will flow in retrograde fashion through the vein and to the capillary bed within the ischemic region of the myocardium. The balloon may remain inflated for a desired period of time to allow the drug or substance to be effectively absorbed by the tissues adjacent to that capillary bed. Thereafter, the balloon is deflated, allowing 20 normal venous flow through the vein. The catheter 112 may be removed after a single dose is delivered or it may remain indwelling for a period of time (e.g., hours, days, weeks or months) to permit repeated doses to be delivered by repeating the foregoing injection procedure. Any or all of the attributes and options described above with respect to the extravascular delivery catheter 12 may also be incorporated into this retrovenous delivery catheter 112, to the extent feasible and 25 ~~not adverse to the intended function of this retrovenous delivery catheter as described herein.~~

25 **D. Catheter Devices For Intramyocardial Delivery of Substances or Articles Via an Endocardial Approach**

Although the following examples relate to applications wherein the penetrating catheter is positioned within a chamber of the heart, it is to be understood that the methods, devices and systems described and claimed in this 30 regard are useable, not only in chambers of the heart, but in any anatomical cavity, lumen or structure that is substantially larger in diameter than the outer diameter of the penetrating catheter used.

Figures 14-19 show embodiments of the invention that may be used for delivery of substances or articles into the myocardial wall via an endocardial approach. In these embodiments, the tissue penetrating catheter 10, 200 or 200a is advanced through the vasculature to a position within a chamber of the heart.

5 Thereafter the penetrator 85, 204 or 206 is advanced from the catheter body 13, 202 or 202a and into the adjacent wall of the heart. A delivery catheter 12 is then advanced through the lumen of the penetrator 85, 204 or 206 and into the myocardium. A desired substance may then be injected through the delivery catheter 12 and onto the myocardium at desired location(s). As explained
10 herebelow, the configuration of the penetrator 85, 204, 206 may control the direction in which the delivery catheter 12 advances. In particular, the penetrator 85, 204 or 206 may be configured such that it directs the delivery catheter 12 in a direction that is substantially or roughly parallel to the adjacent endocardial wall of the myocardium.

15 Referring specifically to Figures 14 and 15, there is shown a catheter system 200 comprising an elongate flexible catheter body 202 having a distal end opening 203 out of which a resilient tissue penetrator 204 is advanceable. The tissue penetrator 204 in the particular embodiment shown comprises a hollow needle. The penetrator 204 that is pre-bent such that a single, gradual 90° bend is formed
20 therein, as shown. In operation, the catheter body 202 is advanced through the vasculature and into a chamber of the heart (e.g., the left ventricle). With the penetrator 204 retracted within the catheter body 202, the distal end DE of the catheter body 202 is placed in abutting contact with, or close to, the endocardial surface of the myocardium. Thereafter, the penetrator 204 is advanced out of the
25 distal end opening 203 and into the myocardium M. The approximate 90° bend formed in the penetrator 204 causes the distal tip of the fully advanced penetrator 204 to be aimed in a direction that is generally perpendicular to the longitudinal axis of the catheter body 202 and generally parallel to the endocardial surface of the myocardium. The delivery catheter 12 is then advanced through the lumen or bore of the hollow penetrator 204, out of the distal end of the penetrator 204 and through a quantity of myocardial tissue in a direction that is generally parallel to the endocardial surface of the myocardium. The desired drug or substance is then
30

injected through the delivery catheter 12. As described above in relation to another embodiment, it is possible to create a continuous trail of substance or a plurality of spaced-apart substance deposition sites by slowly withdrawing or advancing the delivery catheter 12 while continuously or periodically injecting the desired 5 substance through the delivery catheter. If subsequent dosing or later delivery of substance or apparatus is desired, the penetrator 204 may be retracted into the catheter body 202 and the penetrating catheter 200 may be removed, leaving the delivery catheter 12 in place for subsequent use.

With specific reference to Figure 16, there is shown an alternative or 10 modified embodiment of the catheter system 200a wherein the tissue penetrator 206 comprises a resilient hollow needle that is preformed to a helical or corkscrew configuration. As in the embodiment shown in Figures 14-15, the catheter body 202a is advanced into a chamber of the heart and maneuvered to a position where its distal end is in abutment with or close-spaced to the endocardial surface of the 15 myocardium. Thereafter, the penetrator 206 is advanced out of the catheter's distal opening 203a and the penetrator 206 is rotated as it is advanced into the myocardium. The rotation of the penetrator 206 as it is advanced causes the corkscrew penetrator 206 to essentially screw into the myocardium. The delivery catheter 12 is then advanced through the lumen of the penetrator and into the 20 myocardium where it is used, in the manner described above, to deliver the desired substance in a desired deposition area 207 (e.g., a trail, elongate track, series of depots or deposits, in a line, etc.) It will be appreciated that, in this embodiment, after-one-deposition-area-207-has-been-created; the delivery catheter 12 may be retracted into the lumen of the penetrator 206 and the penetrator 206 may be 25 rotated to a new position, at which time the delivery catheter may once again be advanced into an area of myocardial tissue that is different from the area into which the delivery catheter had been previously advanced. In this manner, an array of substance deposition patterns 207 may be formed in a substantial 360° radius around the central axis of the corkscrew penetrator 206 as illustrated in Figure 16a. 30 If subsequent dosing or later delivery of substance or apparatus is desired, the penetrator 206 may be rotatably retracted into the catheter body 202a and the

penetrating catheter 200a may be removed, leaving the delivery catheter 12 in place for subsequent use.

Figure 17 shows an example of the use of a side exiting penetrating catheter system 10a that is a modification of that type shown in Figures 2 and 2a. This 5 catheter system is also useable to accomplish the delivery of a substance into the myocardial wall, via an endocardial approach. In the example shown in Figure 17, the tissue penetrating catheter 10a comprises a catheter body 13a which may be the same or similar to that shown in Figures 2 and 2a or may be constructed in any suitable manner known in the art of catheter design and construction. A penetrator 10 exit port 37a is formed in the catheter body 13a and a curved penetrator 85a comprising a hollow needle is advanceable from the exit port 37a as shown in the example of Figure 17. An optional guide catheter may be used to guide the penetrating catheter to a position adjacent the wall of the atrium or ventricle in the area where it is desired to deliver the substance (or article). In operation, the 15 penetrating catheter body 13 is maneuvered into juxtaposition with the endocardial surface of the myocardium, with or without the use of the optional guide catheter 210. The penetrating catheter 10a is then placed in a rotational orientation whereby the side exit port 37a is aimed at or directly juxtaposed with the endocardial surface to be penetrated. Optional rotational-orientation-indicating 20 markers on the catheter body 13a, imaging apparatus (on board the catheter body 13a or located elsewhere), electro-anatomical catheter navigation systems or other apparatus for discerning the specific rotational orientation of the catheter relative to the trajectory or path upon which the penetrator 85a will advance, may be used as described above and in the prior patent applications incorporated herein by 25 reference. After the exit port 37a has been positioned in juxtaposition to the endocardial surface, the penetrator 85a is advanced into the adjacent myocardial tissue. The curve(s) and shape of the penetrator 85a are such that as it advances it reaches a position where its distal tip is directed generally parallel to the endocardial surface, as shown in Figure 17. Thereafter, the delivery catheter 12 30 is advanced through the penetrator 85a and into the myocardium. As in the other embodiments described above, the positioning and shape of the penetrator causes the delivery catheter to advance on a path that does not result in the delivery

catheter a) repuncturing through the endocardium and into the chamber of the heart or b) passing outwardly through the epicardial surface of the heart and/or c) perforating a substantially sized coronary blood vessel in a manner that would cause untoward bleeding or other potential complications. The substance (or 5 article) is then injected through the delivery catheter and into the myocardium. As described above in relation to the other embodiments, it is possible to create multiple spaced-apart intramyocardial depots of a substance or a continuous, elongate depot of the substance by slowly advancing or retracting the delivery catheter 85a while continuously or periodically injecting the desired substance. If 10 subsequent dosing or later delivery of substance or apparatus is desired, the penetrator 85a may be retracted into the catheter body 13a and the penetrating catheter 10 may be removed, leaving the delivery catheter 12 in place for subsequent use.

Figures 18 and 19 show an example of a procedure wherein a therapeutic substance (e.g., myoblasts, angiogenic factors, muscle grafts, etc.) may be deposited directly into an infarct zone IZ wherein myocardial tissue has become necrotic. In this example, the penetrating catheter 10 has been advanced into a coronary vein CV adjacent to the infarct zone IZ. A penetrator 85 having an approximate 90 degree curvature is advanced from the penetrating catheter 10, 15 though the wall of the coronary vein CV and into or near the infarct zone IZ. The delivery catheter 12 is then advanced through the lumen of the penetrator 85 and through all or a portion of the infarct zone, as specifically shown in Figure 19. Thereafter, as the therapeutic substance is being injected through the delivery catheter 12, the delivery catheter 12 is slowly retracted in the proximal direction 20 (see arrows on Figure 19), thereby providing an elongate deposition pattern DP wherein the therapeutic substance is deposited. In addition to the area where the delivery catheter 12 is being used to deposit the therapeutic substance, Figure 19 also illustrates a previously created deposition pattern DP (see cross-hatched area 25 on Figure 19). This previously created deposition pattern DP is an elongate region, as shown. A deposition pattern axis DPA projected through the elongate deposition pattern DP is non-perpendicular and preferable tangential or nearly tangential to the adjacent endocardial surfaces of the right and left ventricles RV, LV. As explained 30

hereabove, this generally tangential or non-perpendicular approach allows a greater length of delivery catheter 12 to be advanced into the myocardium than would have been possible if the penetrator 85 had been aimed or directed such that the delivery catheter 12 advanced perpendicular to and toward the left or right ventricle LV, RV.

5

The procedure illustrated in Figures 18-19 may be used to revitalize or restore function to regions of the myocardium that are necrotic or severely damaged. Thus, this technique may be useable to treat congestive heart failure. In addition to the deposition of myoblasts, stem cells, other cellular preparations, 10 angiogenic factors, drugs or other therapeutic substances intended to improve the contractility or function of the impaired myocardium, this technique may also be used to implant grafts of muscle tissue into the myocardium. In this regard, a coring needle may be used to harvest an elongate segment of healthy cardiac or other muscle tissue. That harvested tissue graft may then be loaded into the 15 delivery catheter 12 and deposited into the infarct zone IZ as the delivery catheter 12 is retracted, thereby creating an elongate tissue graft that extends fully or partially through the infarct zone IZ.

Although exemplary embodiments of the invention have been shown and described, many changes, modifications and substitutions may be made by those 20 having ordinary skill in the art without necessarily departing from the spirit and scope of this invention. Specifically, elements or attributes described in connection with one embodiment may also be used in connection with another embodiment provided that the inclusion or use of such element or attribute would not render the embodiment in which it is incorporated unuseable or otherwise undesirable for an 25 intended application. Accordingly, all such additions, deletions, modifications and variations to the above-described embodiments are to be included within the scope of the following claims.

CLAIMS

What is claimed is:

1. 1. A system for delivering substances or apparatus to an extravascular target site within the body of a human or veterinary patient, said system comprising:
 2. a. a vessel wall penetrating catheter that comprises i) a catheter body that is insertable into the vasculature of the patient and ii) a vessel wall penetrating member having a lumen extending longitudinally therethrough, said penetrating member being passable from the catheter body and through the wall of a blood vessel in which the catheter body is positioned; and,
 3. b. a delivery catheter having a lumen extending longitudinally therethrough, said delivery catheter being advanceable through the lumen of the vessel wall penetrating member to an extravascular target site;
 4. said vessel wall penetrating member being retractable into the catheter body of the vessel wall penetrating catheter and the vessel wall penetrating catheter being removable from the patient's body such that the delivery catheter remains indwelling with the distal end of the delivery catheter located at the extravascular target site.
2. 2. A system according to Claim 1 wherein the vessel wall penetrating catheter further comprises iii) a guidance element useable by the operator to position the vessel wall penetrating catheter body within the vasculature of the patient such that when the vessel wall penetrating member is passed from the catheter body it will penetrate through the wall of the blood vessel in the direction of the intended extravascular target site.

- 1 3. A system according to Claim 2 wherein the guidance element comprises an
- 2 imaging apparatus.

- 1 4. A system according to Claim 3 wherein the imaging apparatus is an
- 2 ultrasound imaging apparatus.

- 1 5. A system according to Claim 2 wherein the guidance element comprises an
- 2 imageable marker on the vessel wall penetrating catheter body.

- 1 6. A system according to Claim 2 wherein the guidance element comprises the
- 2 combination of an imaging apparatus and at least one imageable marker that is
- 3 imageable by the imaging apparatus.

- 1 7. A system according to Claim 2 wherein the guidance element comprises an
- 2 emitter located on or in the catheter body, said emitter emitting a signal that is
- 3 received by an extracorporeally situated signal-receiving apparatus.

- 1 8. A system according to Claim 1 wherein the delivery catheter further
- 2 comprises a matter blocking member for preventing cellular ingrowth and other
- 3 matter from obstructing the lumen of the delivery catheter.

- 1 9. A system according to Claim 8 wherein the delivery catheter has an outflow
- 2 opening through which substances may pass out of the lumen of the delivery
- 3 catheter and into the target location and wherein the matter blocking member
- 4 comprises a selectively permeable barrier that allows desired substances to be
- 5 infused in the distal direction through the outflow opening and to the target location
- 6 but prevents cellular ingrowth and other matter from entering the lumen of the
- 7 delivery catheter through said outflow opening.

- 1 10. A system according to Claim 9 wherein the selectively permeable barrier is
- 2 a balloon attached to the delivery catheter such that substances infused through

1 the lumen of the delivery catheter collect within the balloon and subsequently
2 diffuse outwardly through the balloon.

1 11. A system according to Claim 8 wherein the matter blocking member
2 comprises a stylet that is insertable into the lumen of the delivery catheter to block
3 the entry of extraneous matter thereinto.

1 12. A system according to Claim 11 wherein the stylet is removable from the
2 lumen of the delivery catheter to permit delivery of a substance or apparatus
3 through the delivery catheter.

1 13. A system according to Claim 1 wherein the delivery catheter comprises:
2 a first tube having a lumen and a sidewall in which an outflow aperture is
3 formed; and,
4 a second tube rotatably disposed in a coaxial position within the first tube,
5 said second tube having a lumen, a closed distal end and a sidewall in which an
6 opening is formed;
7 the second tube being rotatably moveable between i) a blocking position
8 wherein the side wall of the second tube substantially blocks the outflow aperture
9 of the first tube to prevent cellular ingrowth and other matter from entering the
10 lumen of the second tube and ii) an infusion position wherein the opening of the
11 second tube is aligned with the outflow opening of the first tube such that a
12 substance-that-is-injected-into-the-lumen-of-the-second-tube-will-flow-through the
13 opening of the second tube and through the outflow opening of the first tube.

1 14. A system according to Claim 12 wherein a plurality of outflow apertures are
2 formed in the sidewall of the first tube.

1 15. A system according to Claim 1 wherein the delivery catheter comprises:
2 a tube having a lumen and a sidewall in which an outflow aperture is formed;
3 and,

4 an obturator member disposed at least partially within the lumen of the tube,
5 said obturator member being alternately disposable in i) a blocking position wherein
6 the obturator substantially blocks the outflow aperture of the tube to prevent cellular
7 ingrowth and other matter from entering the lumen of the tube and ii) an infusion
8 position wherein the obturator does not substantially block the outflow apertures
9 such that fluid may be injected through the lumen of the tube and out of the outflow
10 aperture.

1 16. A system according to Claim 15 wherein a plurality of outflow apertures are
2 formed in the sidewall of the tube.

1 17. A system according to Claim 15 wherein the obturator member is an
2 inflatable balloon that assumes said blocking position when inflated and said
3 infusion position when deflated.

1 18. A system according to Claim 1 wherein the delivery catheter comprises an
2 infusion lumen, a return lumen, an outflow aperture through which infused
3 substances may flow out of the infusion lumen and a flow diverter, said flow diverter
4 that is alternately deployable in i) an infusion position whereby substances infused
5 through the infusion lumen will flow out of the outflow aperture and ii) a recirculation
6 position whereby fluid infused through the infusion lumen will be recirculated back
7 through the return lumen.

1 19. A system according to Claim 1 wherein the delivery catheter comprises a
2 pressure increasing outflow opening configured to cause an increase the pressure
3 of fluids that are injected through the delivery catheter lumen and out of said
4 pressure increasing outflow opening.

1 20. A system according to Claim 19 wherein said pressure increasing outflow
2 opening is formed in the side wall of the delivery catheter.

- 1 21. A system according to Claim 20 wherein a plurality of pressure increasing
- 2 outflow openings are formed in the side wall of the delivery catheter.
- 1 22. A system according to Claim 1 wherein the delivery catheter further
- 2 comprises an anchoring member for anchoring the catheter in a substantially fixed
- 3 position within the patient's body.
- 1 23. A system according to Claim 22 wherein the anchoring member is selected
- 2 from the group of anchoring members consisting of:
 - 3 a hook;
 - 4 a barb;
 - 5 a permeable surface into which tissue may grow;
 - 6 an adhesive; and,
 - 7 combinations thereof.
- 1 24. A system according to Claim 1 wherein the delivery catheter further
- 2 comprises a backflow deterrent member for blocking backflow of substances that
- 3 have been injected through the delivery catheter.
- 1 25. A system according to Claim 24 wherein said backflow deterrent member
- 2 comprises a backflow barrier rib formed on the delivery catheter.
- 1 26. A system according to Claim 25 wherein said backflow barrier comprises an
- 2 inflatable balloon on the delivery catheter.
- 1 27. A system according to Claim 25 wherein said backflow barrier comprises a
- 2 raised projection formed on the exterior of the delivery catheter.
- 1 28. A system according to Claim 27 wherein the raised projection comprises an
- 2 annular rib formed about the outer surface of the delivery catheter

- 1 29. A system according to Claim 24 wherein the backflow deterrent comprises
- 2 a sealant that is implanted prior to or concurrently with removal of the delivery
- 3 catheter so as to prevent the injected substance from bacflowing through the tract
- 4 from which the delivery catheter is removed.
- 1 30. A system according to Claim 29 wherein the sealant comprises a quantity
- 2 of a flowable sealant injected into the tract upon removal of the delivery catheter.
- 1 31. A system according to Claim 29 wherein the sealant comprises a detachable
- 2 sealing member.
- 1 32. A system according to Claim 31 wherein the detachable sealing member is
- 2 formed of biodegradable material.
- 1 33. A system according to Claim 32 wherein the sealing member is a collagen
- 2 sponge.
- 1 34. A system according to Claim 32 wherein the sealing member is a hydrogel
- 2 sponge.
- 1 35. A system according to Claim 1 wherein at least a portion of the delivery
- 2 catheter is coated with an adhesive.
- 1 36. A system according to Claim 1 wherein an anti-microbial substance is
- 2 disposed on at least a portion of the delivery catheter.
- 1 37. A system according to Claim 1 wherein an anti-coagulant substance is
- 2 disposed on at least a portion of the delivery catheter.
- 1 38. A system according to Claim 1 further comprising apparatus for creating a
- 2 pocket within tissue adjacent to the delivery catheter such that when a substance

1 or apparatus is introduced through the delivery catheter it will be received within
2 said pocket.

1 39. A system according to Claim 38 wherein the apparatus for creating a pocket
2 comprises an energy emitting member that emits energy into adjacent tissue to
3 create said pocket.

1 40. A system according to Claim 39 wherein the energy emitting apparatus is a
2 radiofrequency electrode.

1 41. A system according to Claim 39 wherein the energy emitting apparatus is a
2 laser.

1 42. A system according to Claim 38 wherein the apparatus for creating a pocket
2 comprises a nozzle through which a stream of fluid may be injected to create the
3 pocket in adjacent tissue.

1 43. A system according to Claim 38 wherein the apparatus for creating a pocket
2 comprises an expandable cage which, when expanded, creates said pocket.

3

4 44. A system according to Claim 1 further in combination with an infusion
5 apparatus for infusing a substance through the delivery catheter.

1 45. A system according to Claim 44 wherein said infusion apparatus is a syringe.

1 46. A system according to Claim 44 wherein said infusion apparatus is a pump.

1 47. A system according to Claim 44 wherein said infusion apparatus is a
2 reservoir positioned for gravity drainage of the substance through the delivery
3 catheter.

- 1 48. A system according to Claim 44 wherein said infusion apparatus further
- 2 comprises a quantity of a substance for infusion through the delivery catheter.
- 1 49. A system according to Claim 48 wherein the substance is a drug.
- 1 50. A system according to Claim 49 wherein the drug is selected from the group
- 2 consisting of: thrombolytics, platelet inhibitors, anti-restenotic agents, beta
- 3 adrenergic blockers, ion channel antagonists, positive or negative ionotropic
- 4 agents, anti-arrhythmics and combinations thereof.
- 1 51. A system according to Claim 48 wherein the substance is a protein.
- 1 52. A system according to Claim 48 wherein the substance is an angiogenic
- 2 substance.
- 1 53. A system according to Claim 51 wherein the angiogenic substance is
- 2 selected from the group consisting of vascular endothelial growth factor (VEGF),
- 3 fibroblast growth factors (FGF), epidermal growth factor (EGF), platelet-derived
- 4 growth factor (PDGF), hepatocyte growth factor (HGF) or scatter factor, heparin
- 5 combined with an adenosine receptor agonist, and combinations thereof.
- 1 54. A system according to Claim 48 wherein the substance comprises cells.
- 1 55. A system according to Claim 54 wherein the substance comprises
- 2 progenitor cells for a type of cell that is desired to be formed at the target site.
- 1 56. A system according to Claim 55 wherein said substance comprises
- 2 myoblasts to form cardiac muscle cells.
- 1 57. A system according to Claim 56 wherein said cells are selected from the
- 2 group consisting of stem cells, progenitor cells, myoblasts, myocytes, secretory
- 3 cells, pancreatic islet cells, dopamine secreting cells, endothelial cells, hepatocytes,

1 cloned cells, cells grown in cell culture, genetically modified cells, and combinations
2 thereof.

1 58. A system according to Claim 48 wherein the substance is a gene.

1 59. A system according to Claim 48 wherein the substance comprises a gene
2 and a vector for facilitating entry of the gene into locations within cells at which the
3 gene will have a desired effect on the cells.

1 60. A system according to Claim 59 wherein the vector is a virus.

1 61. A method for delivering a substance or apparatus to an extravascular target
2 site within the body of a human or veterinary patient, said method comprising the
3 steps of:

4

5 (A) providing a vessel wall penetrating catheter that is insertable into the
6 vasculature of the patient, said vessel wall penetrating catheter
7 having a penetrating member that is advanceable through the wall of
8 a blood vessel in which the catheter body is positioned, said vessel
9 wall penetrating member having a lumen extending longitudinally
10 therethrough;

11

12 (B) inserting the vessel wall penetrating catheter into the vasculature of
13 the patient;

14

15 (C) positioning the vessel wall penetrating catheter within the vasculature
16 of the patient such that the penetrator, when advanced, will pass
17 through the wall of a blood vessel to a location near the target site;

18

19 (D) advancing the penetrator through the wall of a blood vessel and to
20 a location near the target site;

21

22 (E) advancing through the lumen of the penetrator and to the target site,
23 a second apparatus selected from the group consisting of:
24 i. an elongate delivery catheter having a lumen through
25 which a substance may be injected or withdrawn;
26 ii. an elongate member that comprises a therapeutic
27 apparatus operative to deliver a therapy to the target
28 site;
29 iii. an elongate member that comprises an information-
30 obtaining apparatus operative to obtain information
31 from the target site; and,
32 iv. possible combinations thereof.

1 62. A method according to Claim 61 wherein the vessel wall penetrating catheter
2 further comprises a guidance element useable by the operator to position the
3 vessel wall penetrating catheter body within the vasculature of the patient such that
4 when the vessel wall penetrating member is passed from the catheter body it will
5 penetrate through the wall of the blood vessel in the direction of the intended
6 extravascular target site, and wherein Step C further comprises using said guidance
7 element to position the vessel wall penetrating catheter body within the vasculature
8 of the patient such that when the vessel wall penetrating member is passed from
9 the catheter body it will penetrate through the wall of the blood vessel in the
10 direction of the intended extravascular target site.

1 63. A method according to Claim 62 wherein the guidance element comprises
2 an imaging apparatus and wherein Step C further comprises using the imaging
3 apparatus to image at least the target site and using such image to guide the
4 positioning of the vessel wall penetrating catheter.

1 64. A method according to Claim 63 wherein the imaging apparatus is an
2 ultrasound imaging apparatus and the image used in Step C is an ultrasound
3 image.

- 1 65. A method according to Claim 62 wherein the guidance element comprises
2 indicia that indicates the path that will be followed by the penetrator when it is
3 subsequently advanced from the catheter penetrating catheter and wherein Step
4 C further comprises obtaining an image of the imageable marker and using such
5 image to guide the positioning of the vessel wall penetrating catheter.
- 1 66. A method according to Claim 65 wherein the guidance element comprises
2 the combination of an imaging apparatus and at least one imageable marker on the
3 vessel wall penetrating catheter, and wherein Step C further comprises using the
4 imaging apparatus to obtain an image of at least the imageable marker and using
5 that image to guide the positioning of the vessel wall penetrating catheter.
- 1 67. A method according to Claim 66 wherein the imageable marker provides an
2 indication of the direction in which the penetrator will advance and wherein Step C
3 further comprises imaging of the imageable marker to obtain an indication of the
4 direction in which the penetrator will advance and using said indication to
5 rotationally orient and position the vessel wall penetrating catheter such that
6 subsequent advancement of the penetrator will cause the penetrator to travel in the
7 direction of the target site.
- 1 68. A method according to Claim 62 wherein the guidance element comprises
2 an emitter located on or in the catheter body, said emitter emitting a signal that is
3 received by an extracorporeally situated signal-receiving apparatus and wherein
4 Step C further comprises using an extracorporeally situated signal-receiving
5 apparatus to receive a signal from the emitter and to thereby guide the placement
6 of the vessel wall penetrating catheter.
- 1 69. A method according to Claim 61 wherein the second apparatus comprises
2 an elongate delivery catheter having a lumen through which a substance may be
3 delivered and wherein the method further comprises the step of:
4 (F) delivering a substance through the delivery catheter to the target site.

1 70. A method according to Claim 69 wherein the delivery catheter is a delivery
2 catheter having an outer diameter of less than 0.5 mm.

1 71. A method according to Claim 69 wherein the delivery catheter further
2 comprises a matter blocking member for preventing cellular ingrowth and other
3 matter from obstructing the lumen of the delivery catheter and wherein the method
4 further comprises the step of:

5 using said matter blocking member to prevent cellular ingrowth
6 and other matter from obstructing the lumen of the delivery catheter
7 at least during times when no substance is being infused through the
8 delivery catheter.

1 72. A method according to Claim 71 wherein the delivery catheter has an outflow
2 opening through which substances may pass out of the lumen of the delivery
3 catheter and into the target location and wherein the matter blocking member
4 comprises a selectively permeable barrier that allows desired substances to be
5 infused in the distal direction through the outflow opening and to the target location
6 but prevents cellular ingrowth and other matter from entering the lumen of the
7 delivery catheter through said outflow opening, and wherein the method further
8 comprises the step of:

9 infusing a substance in the distal direction through the delivery
10 catheter and, thereafter, allowing the substance to pass outwardly
11 through the selectively permeable barrier.

1 73. A method according to Claim 71 wherein the selectively permeable barrier
2 comprises a balloon attached to the delivery catheter and wherein the method
3 further comprises the step of:

4 infusing a substance the distal direction through the delivery
5 catheter such that the substance collects within the balloon and
6 subsequently diffuses outwardly through the balloon.

1 74. A method according to Claim 71 wherein the matter blocking member
2 comprises a stylet that is insertable into the lumen of the delivery catheter to block
3 cellular ingrowth and other matter from entering thereinto and wherein the method
4 further comprises the step of:

5 inserting the stylet into the lumen of the delivery catheter at
6 least at times when no substance is being infused through said
7 lumen, thereby blocking the entry of cellular ingrowth and other
8 matter into the delivery catheter lumen.

1 75. A method according to Claim 74 wherein the stylet is removable from the
2 lumen of the delivery catheter to permit delivery of a substance or apparatus
3 through the delivery catheter and wherein the method further comprises the step
4 of:

5 removing the stylet from the delivery catheter lumen when it is
6 desired to deliver a substance or apparatus through the delivery
7 catheter lumen.

1 76. A method according to Claim 69 wherein the delivery catheter comprises:
2 a first tube having a lumen and a sidewall in which an outflow aperture is
3 formed; and;
4 a second tube rotatably disposed in a coaxial position within the first tube,
5 said second tube having a lumen, a closed distal end and a sidewall in which an
6 opening is formed;
7 the second tube being rotatably moveable between i) a blocking position
8 wherein the side wall of the second tube substantially blocks the outflow aperture
9 of the first tube to prevent cellular ingrowth and other matter from entering the
10 lumen of the second tube and ii) a delivery position wherein the opening of the
11 second tube is aligned with the outflow opening of the first tube such that a
12 substance that is injected into the lumen of the second tube will flow through the
13 opening of the second tube and through the outflow opening of the first tube, and
14 wherein said method further comprises the steps of:

15 placing the second tube in the blocking position when no
16 substance or apparatus is being delivered through the delivery
17 catheter; and,

18 placing the second tube in the delivery position when a
19 substance or apparatus is being delivered through the delivery
20 catheter.

1 77. A method according to Claim 71 wherein the delivery catheter comprises:
2 a tube having a lumen and a sidewall in which an outflow aperture is formed;

4 an obturator member disposed at least partially within the lumen of the tube,
5 said obturator member being alternately disposable in i) a blocking position wherein
6 the obturator substantially blocks the outflow aperture of the tube to prevent cellular
7 ingrowth and other matter from entering the lumen of the tube and ii) a delivery
8 position wherein the obturator does not substantially block the outflow apertures
9 such that fluid may be injected through the lumen of the tube and out of the outflow
10 aperture; and wherein the method further comprises the steps of:

11 placing the obturator in the blocking position when no
12 substance or apparatus is being delivered through the delivery
13 catheter; and,

14 placing the obturator in the delivery position when a substance
15 or apparatus is being delivered through the delivery catheter.

1 78. A method according to Claim 77 wherein the obturator member is an
2 inflatable balloon that assumes said blocking position when inflated and said
3 infusion position when deflated, and wherein the step of placing the obturator in the
4 blocking position comprises inflating the balloon and the step of placing the
5 obturator in the delivery position comprises deflating the balloon.

1 79. A method according to Claim 69 wherein the delivery catheter comprises a
2 delivery lumen, a return lumen, an aperture through which substances or apparatus
3 delivered through the delivery lumen may pass out of the delivery catheter and a

4 flow diverter, said flow diverter that is alternately deployable in i) a delivery position
5 whereby substances or apparatus may be delivered through the delivery catheter
6 lumen and out of the aperture and ii) a recirculation position whereby fluid infused
7 through the delivery lumen will be recirculated back through the return lumen and
8 wherein the method further comprises the steps of:

9 placing the diverter in the delivery position when it is desired
10 to deliver a substance or apparatus through the delivery lumen and
11 out of the aperture; and,

12 placing the diverter in the recirculation position and infusing a
13 fluid through the delivery lumen and back through the recirculation
14 lumen, when no substance or apparatus is being delivered through
15 the delivery lumen.

1 80. A method according to Claim 69 wherein the delivery catheter comprises a
2 pressure increasing outflow opening configured to cause an increase the pressure
3 of substances that are injected through the delivery catheter lumen and out of said
4 pressure increasing outflow opening, and wherein the method further comprises the
5 step of:

6 delivering a substance through the delivery catheter and out
7 of the outflow opening such that the pressure of the substance
8 increases as it flows out of the outflow opening.

1 81. A method according to Claim 69 wherein the substance delivered in Step F
2 is a therapeutic substance.

1 82. A method according to Claim 69 wherein the substance delivered in Step F
2 is a agent that provides an enhanced image of the target site.

1 83. A method according to Claim 69 wherein the substance delivered in Step F
2 is a traceable substance that may be used to determine the rate at which the
3 substance distributes away from or is otherwise inactivated at the target site or
4 other pharmacokinetic or biodistributive parameters or variables.

- 1 84. A method according to Claim 81 wherein the therapeutic substance is
- 2 selected from the group consisting of : a drug, a protein, cells, an angiogenic
- 3 substance, a myogenic substance, a neurogenic substance, a gene, a gene therapy
- 4 composition, genetic material in combination with a vector for delivering the genetic
- 5 material into locations within cells at which the genetic material will have a desired
- 6 effect on the cells;

- 1 85. A method according to Claim 81 wherein the method is carried out to
- 2 improve perfusion of an ischemic target site and where the therapeutic substance
- 3 delivered in Step F comprises is an angiogenic agent that increases vascularity of
- 4 the ischemic target site.

- 1 86. A method according to Claim 85 wherein the angiogenic agent delivered in
- 2 Step F is selected from the group of angiogenic agents consisting of vascular
- 3 endothelial growth factor (VEGF), fibroblast growth factors (FGF), epidermal growth
- 4 factor (EGF), platelet-derived growth factor (PDGF), hepatocyte growth factor
- 5 (HGF) or scatter factor, heparin combined with an adenosine receptor agonist, nerve
- 6 cell growth factor (NGF), and combinations thereof.

- 1 87. A method according to Claim 81 wherein the therapeutic substance delivered
- 2 in Step F comprises cells.

- 1 88. A method according to Claim 87 wherein said cells are selected from the
- 2 group consisting of stem cells, progenitor cells, myoblasts, myocytes, secretory
- 3 cells, pancreatic islet cells, dopamine secreting cells, endothelial cells, hepatocytes,
- 4 cloned cells, cells grown in cell culture, genetically modified cells, and combinations
- 5 thereof.

- 1 89. A method according to Claim 87 wherein the method is carried out to treat
- 2 a condition characterized by a deficiency of a type of cell within the patient's body
- 3 and wherein the type of cell that is deficient matures in situ from stem cells, and

1 wherein the therapeutic substance delivered in Step F comprises stem cells of a
2 type that mature into the deficient cell type.

1 90. A method according to Claim 89 wherein the method is carried out to treat
2 a condition characterized by a lack of living myocytes in or near the target site and
3 wherein the therapeutic substance delivered in Step F comprises myocytes.

1 91. A method according to Claim 89 wherein the method is carried out to treat
2 parkinsonism, the target site comprises the substantia nigra of the patient's brain
3 and wherein the therapeutic substance delivered in Step F comprises dopamine
4 secreting cells which when implanted will increase dopamine in the substantia
5 nigra.

1 92. A method according to Claim 91 wherein the dopamine secreting cells
2 comprise fetal dopamine secreting cells.

1 93. A method according to Claim 89 wherein the method is carried out to treat
2 diabetes, the target site comprises the patient's pancreas, and wherein the
3 therapeutic substance delivered in Step F comprises insulin secreting cells which,
4 when implanted, will increase insulin production by the patient's pancreas.

1 94. A method according to Claim 93 wherein the insulin secreting cells comprise
2 pancreatic β -islet cells.

1 95. A method according to Claim 81 wherein the method is carried out to treat
2 a neurogenerative disorder and wherein the substance delivered comprises nerve
3 cells.

1 96. A method according to Claim 81 wherein the method is carried out to treat
2 a neurogenerative disorder and wherein the substance delivered comprises a
3 substance that facilitates nerve growth.

- 1 97. A method according to Claim 96 wherein the substance delivered is selected
- 2 from the group consisting of: glial cell line-derived neurotropic factor (GDNF), nerve
- 3 growth factor, neuro-immunophilin ligand, poly ADP-Ribose polymerase, and
- 4 combinations thereof.

- 1 98. A method according to Claim 81 wherein the therapeutic substance
- 2 comprises a gene in combination with a vector for facilitating entry of the gene into
- 3 locations within cells in which the gene will have a desired therapeutic effect.

- 1 99. A method according to Claim 98 wherein the vector is a virus.

- 1 100. A method according to Claim 61 wherein the second apparatus further
- 2 comprises an anchoring member for holding the second apparatus in a
- 3 substantially fixed position within the patient's body and wherein the method further
- 4 comprises the step of:
 - 5 (F) causing the anchoring apparatus to hold the second apparatus in a
 - 6 substantially fixed position within the patient's body.

- 1 101. A method according to Claim 100 wherein the anchoring member is selected
- 2 from the group of anchoring members consisting of:
 - 3 a hook;
 - 4 a barb;
 - 5 a permeable surface into which tissue may grow;
 - 6 an adhesive; and,
 - 7 combinations thereof;
- 8 and wherein Step F comprises causing the anchoring apparatus to engage
- 9 tissue adjacent thereto so as to hold the second apparatus in said substantially
- 10 fixed position.

- 1 102. A method according to Claim 61 wherein the second apparatus is a delivery
- 2 catheter, wherein the delivery catheter further comprises a backflow deterrent for

3 blocking backflow of substances that have been injected through the delivery
4 catheter and wherein the method further comprises the step of:
5 causing the backflow deterrent to deter backflow of a substance that has
6 been infused through the delivery catheter to the target site.

1 103. A method according to Claim 102 wherein the backflow deterrent comprises
2 a backflow barrier rib formed on the delivery catheter and wherein the step of
3 causing the backflow deterrent to deter backflow is carried out by positioning the
4 backflow deterrent rib so that it acts as a barrier to the unwanted backflow.

1 104. A method according to Claim 103 wherein said backflow barrier comprises
2 an inflatable balloon on the delivery catheter and wherein the step causing the
3 backflow deterrent to deter backflow is carried out by inflating the balloon.

1 105. A method according to Claim 102 wherein said backflow deterrent comprises
2 a raised projection formed on the exterior of the delivery catheter and wherein the
3 step of causing the backflow deterrent to deter backflow is carried out by positioning
4 the raised projection so that it acts as a barrier to the unwanted backflow.

1 106. A method according to Claim 105 wherein the raised projection comprises
2 an annular rib formed about the outer surface of the delivery catheter

1 107. A method according to Claim 102 wherein the backflow deterrent comprises
2 a sealant which, when implanted in the penetration tract through which the delivery
3 catheter was advanced, will prevent the substance from bacflowing through that
4 tract, and wherein Step F of the method comprises implanting the sealant into the
5 penetration tract.

1 108. A method according to Claim 107 wherein the sealant is implanted into the
2 tract prior to removal of the delivery catheter.

- 1 109. A method according to Claim 107 wherein the sealant is implanted into the
- 2 tract prior concurrently with removal of the delivery catheter.

- 1 110. A method according to Claim 107 wherein the sealant comprises a quantity
- 2 of a flowable sealant and wherein the step of implanting the sealant into the
- 3 penetration tract comprises injecting the flowable sealant into the penetration tract.

- 1 111. A method according to Claim 110 wherein the injecting of the flowable
- 2 sealant into the penetration tract comprises injecting the flowable sealant through
- 3 the delivery catheter.

- 1 112. A method according to Claim 107 wherein the sealant comprises a
- 2 detachable sealing member and wherein Step F comprises introducing the sealing
- 3 member into the penetration tract and thereafter detaching the sealing member
- 4 such that it will remain in the penetration tract after the delivery catheter has been
- 5 removed.

- 1 113. A method according to Claim 112 wherein the detachable sealing member
- 2 comprises biodegradable material and wherein Step F comprises introducing the
- 3 biodegradable member into the penetration tract and thereafter detaching the
- 4 biodegradable member such that it will remain in the penetration tract after the
- 5 delivery catheter has been removed.

- 1 114. A method according to Claim 112 wherein the sealing member is a collagen
- 2 sponge and wherein Step F comprises introducing the collagen sponge into the
- 3 penetration tract and thereafter detaching the collagen sponge such that it will
- 4 remain in the penetration tract after the delivery catheter has been removed.

- 1 115. A method according to Claim 112 wherein the sealing member is a hydrogel
- 2 material and wherein Step F comprises introducing the hydrogel material into the
- 3 penetration tract and thereafter detaching the hydrogel material such that it will
- 4 remain in the penetration tract after the delivery catheter has been removed.

1 116. A method according to Claim 61 wherein at least a portion of the second
2 apparatus is coated with an adhesive and wherein the method further comprises
3 the step of:

4 (F) causing the adhesive to adhere to adjacent tissue thereby deterring
5 movement of the second apparatus.

1 117. A method according to Claim 61 wherein an anti-microbial substance is
2 disposed on at least a portion of the second apparatus and wherein the method
3 further comprises the step of:

4 (F) causing the anti-microbial substance to deter microbial growth in the
5 area surrounding the portion of the second apparatus on which the
6 anti-microbial substance is disposed.

1 118. A method according to Claim 61 wherein an anti-coagulant substance is
2 disposed on at least a portion of the second apparatus and wherein the method
3 further comprises the step of:

4 (F) causing the anti-coagulant substance to deter coagulative processes
5 in the area surrounding the portion of the second apparatus on which
6 the anti-coagulant substance is disposed.

1 119. A method according to Claim 69 wherein the apparatus further comprises a
2 tissue pocket-creating-apparatus-and-wherein-the-method-further-comprises the
3 step of:

4 using the tissue pocket creating apparatus to create a pocket within tissue
5 adjacent to the delivery catheter such that when a substance or apparatus is
6 introduced through the delivery catheter it will be received within said pocket

1 120. A method according to Claim 119 wherein the tissue pocket creating
2 apparatus comprises an energy emitting member and wherein the step of using the
3 tissue pocket creating apparatus comprises causing the tissue pocket creating
4 apparatus to emit energy into adjacent tissue to create a tissue pocket therein.

- 1 121. A method according to Claim 120 wherein the energy emitting apparatus is
2 a radiofrequency electrode and wherein the step of using the tissue pocket creating
3 apparatus comprises causing the electrode to emit energy of a magnitude and
4 duration sufficient to create the tissue pocket.

- 1 122. A method according to Claim 120 wherein the energy emitting apparatus is
2 a laser.

- 1 123. A method according to Claim 119 wherein the tissue pocket creating
2 apparatus comprises a nozzle through which a stream of fluid may be injected and
3 wherein the step of using the tissue pocket creating apparatus comprises injecting
4 fluid through the nozzle to create the pocket in adjacent tissue.

- 1 124. A method according to Claim 119 wherein the tissue pocket creating
2 apparatus comprises an expandable cage and wherein the step of using the tissue
3 pocket creating apparatus comprises expanding the cage to create the pocket in
4 adjacent tissue.

- 1 125. A method according to Claim 61 wherein the second apparatus is an
2 elongate member that comprises a therapeutic apparatus operative to deliver a
3 therapy to the target site and wherein the method further comprises the step of:
4 (F) using the therapeutic apparatus to deliver therapy to the target site.

- 1 126. A system for delivery of a substance to a target site located a spaced
2 distance from a blood vessel within the body of a human or animal patient, said
3 system comprising:
4 a vessel wall penetrating catheter that has a vessel wall penetrator
5 advanceable therefrom, said vessel wall penetrating catheter being insertable into
6 the vasculature and positionable in the blood vessel near the target site and said
7 penetrator being thereafter advanceable from the catheter and trough the wall of
8 the blood vessel in the direction of the target site;

9 a delivery catheter that is advanceable through the penetrator and to the
10 target site, said delivery catheter being of sufficient length and constructed such
11 that, after the delivery catheter has been advanced through the penetrator and to
12 the target site, the penetrator may be retracted into the vessel wall penetrating
13 catheter and the vessel wall penetrating catheter may be removed, leaving the
14 delivery catheter in place such that the delivery catheter extends through the
15 patient's vasculature into the blood vessel near the target site, outwardly through
16 the wall of the blood vessel and to the target site.

1 127. A system according to Claim 126 wherein the delivery catheter comprises
2 a hub member that is a) not attached to the proximal end of the delivery catheter
3 while the vessel wall penetrating catheter is being withdrawn and removed and b)
4 attached to the proximal end of the delivery catheter after the vessel wall
5 penetrating catheter has been withdrawn and removed.

1 128. A system according to Claim 126 wherein the delivery catheter further
2 comprises at least one anchoring element for holding the delivery at the target site.

1 129. A system according to Claim 127 wherein the delivery catheter further
2 comprises a barrier for deterring substances injected through the delivery catheter
3 from backflowing around the delivery catheter through the tissue tract through
4 which the delivery catheter extends from the blood vessel to the target site.

1 130. A system according to Claim 126 wherein the delivery catheter further
2 comprises apparatus for preventing cellular ingrowth and other matter from
3 obstructing the lumen of the delivery catheter.

1 131. A system according to Claim 126 wherein the vessel wall penetrating
2 catheter further comprises a guidance element that facilitates positioning and
3 orientation of the vessel wall penetrating catheter within the blood vessel such that,
4 then the penetrator is subsequently advanced from the vessel wall penetrating
5 catheter, the penetrator will travel substantially toward the target site.

1 132. A method for delivery of substances or apparatus to a target site located a
2 spaced distance from a blood vessel within the body of a human or animal patient,
3 said method comprising the steps of:

4 (A) Inserting a vessel wall penetrating catheter into the vasculature of the
5 patient, said vessel wall penetrating catheter having a penetrator
6 advanceable therefrom;

7

8 (B) positioning the vessel wall penetrating catheter in the blood vessel
9 near the target site;

10

11 (C) advancing the penetrator from the vessel wall penetrating catheter
12 and through the wall of the blood in the direction of the target site;

13

14 (D) advancing a delivery catheter through the penetrator and to the target
15 site;

16

17 (E) retracting the penetrator into the vessel wall penetrating catheter;
18 and,

19

20 (F) withdrawing and removing the vessel wall penetrating catheter,
21 leaving the delivery catheter indwelling such that it extends through
22 the patient's vasculature into the blood vessel near the target site,
23 outwardly through the wall of the blood vessel and to the target site.

1 133. A method according to Claim 132 wherein the delivery catheter comprises
2 a hub member that is a) not attached to the proximal end of the delivery catheter
3 while the vessel wall penetrating catheter is being withdrawn and removed and b)
4 attached to the proximal end of the delivery catheter after the vessel wall
5 penetrating catheter has been withdrawn and removed, and wherein the method
6 further comprises the steps of:

7 causing the hub member to be detached from the delivery catheter while the
8 vessel wall penetrating catheter is being withdrawn and removed in Step F; and,
9 causing the hub member to be attached to the proximal end of the delivery
10 catheter after the vessel wall penetrating catheter has been withdrawn and
11 removed in Step F .

1 134. A method according to Claim 132 wherein the delivery catheter further
2 comprises at least one anchoring element for holding the delivery at the target site
3 and wherein the method further comprises:
4 causing the anchoring element to hold the delivery catheter at the target site
5 at least after Step F has been performed.

1 135. A method according to Claim 132 wherein the delivery catheter further
2 comprises a barrier for deterring substances injected through the delivery catheter
3 from backflowing around the delivery catheter through the tissue tract through
4 which the delivery catheter extends from the blood vessel to the target site and
5 wherein the method further comprises:

6 causing the barrier to deter substances injected through the delivery catheter
7 from backflowing around the delivery catheter through the tissue tract through
8 which the delivery catheter extends from the blood vessel to the target site

1 136. A system according to Claim 132 wherein the delivery catheter further
2 comprises apparatus for preventing cellular ingrowth and other matter from
3 obstructing the lumen of the delivery catheter and wherein the method further
4 comprises the step of:

5 causing the apparatus for preventing cellular ingrowth and other matter from
6 obstructing the lumen of the delivery catheter to prevent cellular ingrowth or other
7 matter from obstructing the lumen of the delivery catheter.

8 137. A system according to Claim 126 wherein the vessel wall penetrating
9 catheter further comprises a guidance element that facilitates positioning and
10 orientation of the vessel wall penetrating catheter within the blood vessel such that,
11 then the penetrator is subsequently advanced from the vessel wall penetrating

12 catheter, the penetrator will travel substantially toward the target site and wherein
13 the method further comprises the step of:

14 using the guidance element to position and orient the vessel wall penetrating
15 catheter in the blood vessel prior to performance of Step C such that when Step C
16 is subsequently performed, the penetrator will travel through the blood vessel wall
17 substantially in the direction of the target site.

1 138. A system for delivery of a substance or article to an intramyocardial location
2 in the heart of a mammalian patient, said system comprising:

3 a tissue penetrating catheter that is advanceable through the vasculature to
4 a position within a chamber of the heart;

5 a tissue penetrator having a hollow bore extending therethrough, the
6 penetrator being advancable from the tissue penetrating catheter, through the
7 endocardial surface of the heart and into the myocardium; and,

8 a delivery catheter that is advanceable through the bore of the penetrator
9 and into the myocardial tissue;

0 the substance or article being thereby deliverable through the delivery
1 catheter and into at least one intramyocardial site.

1 139. A system according to Claim 139 wherein the tissue penetrating catheter
2 comprises a flexible catheter body having a distal end and a penetrator outlet port
3 located in the distal end of the catheter body.

1 140. A system according to Claim 139 wherein the tissue penetrating catheter
2 comprises a flexible catheter body having a side wall and a penetrator outlet port
3 located in the side wall of the catheter body.

1 141. A system according to Claim 139 wherein, after the penetrator has been
2 advanced into the myocardium and as the delivery catheter is being advanced
3 through the bore of the penetrator, the configuration and position of the penetrator

4 will cause the delivery catheter to advance through myocardial tissue on a path
5 which does not result in the delivery catheter a) entering any chamber of the heart,
6 b) passing outwardly through the epicardial surface of the heart and/or c)
7 perforating a substantially sized coronary blood vessel in a manner that causes
8 clinically significant bleeding or other clinically significant complications.

1 142. A system according to Claim 138 wherein the vessel wall penetrating
2 catheter further comprises iii) a guidance element useable by the operator to
3 position the vessel wall penetrating catheter body within the vasculature of the
4 patient such that when the vessel wall penetrating member is passed from the
5 catheter body it will penetrate through the wall of the blood vessel in the direction
6 of the intended extravascular target site.

1 143. A system according to Claim 142 wherein the guidance element comprises
2 an imaging apparatus.

1 144. A system according to Claim 143 wherein the imaging apparatus is an
2 ultrasound imaging apparatus.

1 145. A system according to Claim 142 wherein the guidance element comprises
2 an imageable marker on the vessel wall penetrating catheter body.

1 146. A system according to Claim 142 wherein the guidance element comprises
2 the combination of an imaging apparatus and at least one imageable marker that
3 is imageable by the imaging apparatus.

1 147. A system according to Claim 142 wherein the guidance element comprises
2 an emitter located on or in the catheter body, said emitter emitting a signal that is
3 received by an extracorporeally situated signal-receiving apparatus.

- 1 148. A system according to Claim 138 wherein the delivery catheter further
2 comprises a matter blocking member for preventing cellular ingrowth and other
3 matter from obstructing the lumen of the delivery catheter.
- 1 149. A system according to Claim 148 wherein the delivery catheter has an
2 outflow opening through which substances may pass out of the lumen of the
3 delivery catheter and into the target location and wherein the matter blocking
4 member comprises a selectively permeable barrier that allows desired substances
5 to be infused in the distal direction through the outflow opening and to the target
6 location but prevents cellular ingrowth and other matter from entering the lumen of
7 the delivery catheter through said outflow opening.
- 1 150. A system according to Claim 149 wherein the selectively permeable barrier
2 is a balloon attached to the delivery catheter such that substances infused through
3 the lumen of the delivery catheter collect within the balloon and subsequently
4 diffuse outwardly through the balloon.
- 1 151. A system according to Claim 148 wherein the matter blocking member
2 comprises a stylet that is insertable into the lumen of the delivery catheter to block
3 the entry of extraneous matter thereinto.
- 1 152. A system according to Claim 151 wherein the stylet is removable from the
2 lumen of the delivery catheter to permit delivery of a substance or apparatus
3 through the delivery catheter.
- 1 153. A system according to Claim 138 wherein the delivery catheter comprises:
2 a first tube having a lumen and a sidewall in which an outflow aperture is
3 formed; and,
4 a second tube rotatably disposed in a coaxial position within the first tube,
5 said second tube having a lumen, a closed distal end and a sidewall in which an
6 opening is formed;

7 the second tube being rotatably moveable between i) a blocking position
8 wherein the side wall of the second tube substantially blocks the outflow aperture
9 of the first tube to prevent cellular ingrowth and other matter from entering the
10 lumen of the second tube and ii) an infusion position wherein the opening of the
11 second tube is aligned with the outflow opening of the first tube such that a
12 substance that is injected into the lumen of the second tube will flow through the
13 opening of the second tube and through the outflow opening of the first tube.

1 154. A system according to Claim 152 wherein a plurality of outflow apertures are
2 formed in the sidewall of the first tube.

1 155. A system according to Claim 138 wherein the delivery catheter comprises:
2 a tube having a lumen and a sidewall in which an outflow aperture is formed;
3 and,
4 an obturator member disposed at least partially within the lumen of the tube,
5 said obturator member being alternately disposable in i) a blocking position wherein
6 the obturator substantially blocks the outflow aperture of the tube to prevent cellular
7 ingrowth and other matter from entering the lumen of the tube and ii) an infusion
8 position wherein the obturator does not substantially block the outflow apertures
9 such that fluid may be injected through the lumen of the tube and out of the outflow
10 aperture.

1 156. A system according to Claim 155 wherein a plurality of outflow apertures are
2 formed in the sidewall of the tube.

1 157. A system according to Claim 155 wherein the obturator member is an
2 inflatable balloon that assumes said blocking position when inflated and said
3 infusion position when deflated.

1 158. A system according to Claim 138 wherein the delivery catheter comprises
2 an infusion lumen, a return lumen, an outflow aperture through which infused
3 substances may flow out of the infusion lumen and a flow diverter, said flow diverter

4 that is alternately deployable in i) an infusion position whereby substances infused
5 through the infusion lumen will flow out of the outflow aperture and ii) a recirculation
6 position whereby fluid infused through the infusion lumen will be recirculated back
7 through the return lumen.

1 159. A system according to Claim 138 wherein the delivery catheter comprises
2 a pressure increasing outflow opening configured to cause an increase the
3 pressure of fluids that are injected through the delivery catheter lumen and out of
4 said pressure increasing outflow opening.

1 160. A system according to Claim 159 wherein said pressure increasing outflow
2 opening is formed in the side wall of the delivery catheter.

1 161. A system according to Claim 160 wherein a plurality of pressure increasing
2 outflow openings are formed in the side wall of the delivery catheter.

1 162. A system according to Claim 160 wherein the delivery catheter further
2 comprises an anchoring member for anchoring the catheter in a substantially fixed
3 position within the patient's body.

1 163. A system according to Claim 162 wherein the anchoring member is selected
2 from the group of anchoring members consisting of:

3 _____ a hook; _____
4 _____ a barb;
5 _____ a permeable surface into which tissue may grow;
6 _____ an adhesive; and,
7 _____ combinations thereof.

1 164. A system according to Claim 138 wherein the delivery catheter further
2 comprises a backflow deterrent member for blocking backflow of substances that
3 have been injected through the delivery catheter.

- 1 165. A system according to Claim 164 wherein said backflow deterrent member
- 2 comprises a backflow barrier rib formed on the delivery catheter.

- 1 166. A system according to Claim 165 wherein said backflow barrier comprises
- 2 an inflatable balloon on the delivery catheter.

- 1 167. A system according to Claim 165 wherein said backflow barrier comprises
- 2 a raised projection formed on the exterior of the delivery catheter.

- 1 168. A system according to Claim 167 wherein the raised projection comprises
- 2 an annular rib formed about the outer surface of the delivery catheter

- 1 169. A system according to Claim 164 wherein the backflow deterrent comprises
- 2 a sealant that is implanted prior to or concurrently with removal of the delivery
- 3 catheter so as to prevent the injected substance from bacflowing through the tract
- 4 from which the delivery catheter is removed.

- 1 170. A system according to Claim 169 wherein the sealant comprises a quantity
- 2 of a flowable sealant injected into the tract upon removal of the delivery catheter.

- 1 171. A system according to Claim 169 wherein the sealant comprises a
- 2 detachable sealing member.

- 1 172. A system according to Claim 171 wherein the detachable sealing member
- 2 is formed of biodegradable material.

- 1 173. A system according to Claim 172 wherein the sealing member is a collagen
- 2 sponge.

- 1 174. A system according to Claim 172 wherein the sealing member is a hydrogel
- 2 sponge.

- 1 175. A system according to Claim 138 wherein at least a portion of the delivery catheter is coated with an adhesive.
- 1 176. A system according to Claim 138 wherein an anti-microbial substance is disposed on at least a portion of the delivery catheter.
- 1 177. A system according to Claim 138 wherein an anti-coagulant substance is disposed on at least a portion of the delivery catheter.
- 1 178. A system according to Claim 138 further comprising apparatus for creating a pocket within tissue adjacent to the delivery catheter such that when a substance or apparatus is introduced through the delivery catheter it will be received within said pocket.
- 1 179. A system according to Claim 178 wherein the apparatus for creating a pocket comprises an energy emitting member that emits energy into adjacent tissue to create said pocket.
- 1 180. A system according to Claim 179 wherein the energy emitting apparatus is a radiofrequency electrode.
- 1 181. A system according to Claim 179 wherein the energy emitting apparatus is a laser.
- 1 182. A system according to Claim 178 wherein the apparatus for creating a pocket comprises a nozzle through which a stream of fluid may be injected to create the pocket in adjacent tissue.
- 1 183. A system according to Claim 178 wherein the apparatus for creating a pocket comprises an expandable cage which, when expanded, creates said pocket.

- 1 184. A system according to Claim 138 further in combination with an infusion
- 2 apparatus for infusing a substance through the delivery catheter.

- 1 185. A system according to Claim 184 wherein said infusion apparatus is a
- 2 syringe.

- 1 186. A system according to Claim 184 wherein said infusion apparatus is a pump.

- 1 187. A system according to Claim 184 wherein said infusion apparatus is a
- 2 reservoir positioned for gravity drainage of the substance through the delivery
- 3 catheter.

- 1 188. A system according to Claim 184 wherein said infusion apparatus further
- 2 comprises a quantity of a substance for infusion through the delivery catheter.

- 1 189. A system according to Claim 188 wherein the substance is a drug.

- 1 190. A system according to Claim 189 wherein the drug is selected from the
- 2 group consisting of: thrombolytics, platelet inhibitors, anti-restenotic agents, beta
- 3 adrenergic blockers, ion channel antagonists, positive or negative ionotropic
- 4 agents, anti-arrhythmics and combinations thereof.

- 1 191. A system according to Claim 188 wherein the substance is a protein.

- 1 192. A system according to Claim 188 wherein the substance is an angiogenic
- 2 substance.

- 1 193. A system according to Claim 191 wherein the angiogenic substance is
- 2 selected from the group consisting of vascular endothelial growth factor (VEGF),
- 3 fibroblast growth factors (FGF), epidermal growth factor (EGF), platelet-derived
- 4 growth factor (PDGF), hepatocyte growth factor (HGF) or scatter factor, heparin
- 5 combined with an adenosine receptor agonist, and combinations thereof.

- 1 194. A system according to Claim 188 wherein the substance comprises cells.
- 1 195. A system according to Claim 194 wherein the substance comprises progenitor cells for a type of cell that is desired to be formed at the target site.
- 1 196. A system according to Claim 195 wherein said substance comprises myoblasts to form cardiac muscle cells.
- 1 197. A system according to Claim 196 wherein said cells are selected from the group consisting of stem cells, progenitor cells, myoblasts, myocytes, secretory cells, pancreatic islet cells, dopamine secreting cells, endothelial cells, hepatocytes, cloned cells, cells grown in cell culture, genetically modified cells, and combinations thereof.
- 1 198. A system according to Claim 188 wherein the substance is a gene.
- 1 199. A system according to Claim 198 wherein the substance comprises a gene and a vector for facilitating entry of the gene into locations within cells at which the gene will have a desired effect on the cells.
- 1 200. A system according to Claim 199 wherein the vector is a virus.
- 1 201. A system according to Claim 138 wherein the penetrator is of a helical configuration and is capable of being rotated as it is advanced into the myocardial tissue.
- 1 202. A method for delivering a substance or article to one or more intramyocardial sites in the heart of a mammalian patient, the method comprising the steps of:
 - 3 A. providing a tissue penetrating catheter system that comprises i) a catheter that is advanceable through the vasculature to a position within a chamber of the heart, ii) a tissue penetrator having a hollow bore extending therethrough, the

1 penetrator being advancable from the tissue penetrating catheter, and iii) a delivery
2 catheter that is advanceable through the bore of the penetrator and out of the
3 penetrator into myocardial tissue;

4 B. inserting the tissue penetrating catheter into the patient's vasculature
5 and advancing the catheter to a position where the location on the catheter from
6 which the teissue penetrator advances is located within a chamber of the patient's
7 heart;

8 C. advancing the tissue penetrator from the catheter, through the
9 endocardium and into the myocardium;

10 D. advancing the delivery catheter through the bore of the penetrator and
11 into the mycardial tissue; and,

12 E. delivering the substance or article though the delivery catheter and
13 into said one or more intramyocardial sites.

1 203. A method according to Claim 202 wherein the penetrator is curved and
2 wherein Step C further comprises advancing the curved penetrator to a position
3 within the myocardium such that subsequent performance of Step D will not cause
4 the delivery catheter to a) enter any chamber of the heart, b) pass outwardly
5 through the epicardial surface of the heart and/or c) perforate any substantially
6 sized coronary blood vessel in a manner that causes clinically significant bleeding
7 or other clinically significant complications.

1 204. A method according to Claim 203 wherein the penetrator is helically shaped
2 and wherein Step C further comprises rotating the penetrator.

1 205. A method according to Claim 203 further comprising the steps of:

2 F. retracting the delivery catheter into the bore of the penetrator;

3 G. repositioning the penetrator;

4 H. readvancing the delivery catheter through the bore of the repositioned
5 penetrator and into the myocardium; and,

6 I. delivering the substance or article though the delivery catheter and
7 into said one or more additional intramyocardial sites that are different from the one

- 1 or more intramyocardial sites into which the substance or article was delivered in
- 2 Step E.

- 1 206. A method according to Claim 205 wherein Steps F through G are repeated
- 2 a plurality of times.

- 1 207. A method according to Claim 203 wherein Steps D and E further comprise
- 2 advancing the delivery catheter while periodically injecting the substance or article
- 3 so as to deliver the substance or article into a plurality of spaced-apart
- 4 intramyocardial sites.

- 1 208. A method according to Claim 203 wherein Step E further comprises
- 2 retracting the delivery catheter while periodically injecting the substance or article
- 3 so as to deliver the substance or article into a plurality of spaced-apart
- 4 intramyocardial sites.

- 1 209. A method according to Claim 203 wherein Steps D and E further comprise
- 2 advancing the delivery catheter while substantially continually injecting the
- 3 substance or article so as to deliver a trail of the substance or article within the
- 4 myocardial tissue.

- 1 210. A method according to Claim 203 wherein Step E further comprises
- 2 retracting the delivery catheter while substantially continually injecting the
- 3 substance or article so as to deliver a trail of the substance or article within the
- 4 myocardial tissue.

- 1 211. A method according to Claim 203 wherein the penetrating catheter further
- 2 comprises a guidance element useable by the operator to position the penetrating
- 3 catheter body within the chamber of the heart vasculature of the heart such that
- 4 when the penetrator is advanced from the catheter body it will penetrate through the

1 endocardial surface and into the myocardium, and wherein Step C further
2 comprises using said guidance element to position the penetrating catheter body
3 within the chamber of the heart such that when the penetrator is advanced from the
4 catheter body it will penetrate through the endocardium and into the myocardium.
5

1 212. A method according to Claim 211 wherein the guidance element comprises
2 an imaging apparatus and wherein Step C further comprises using the imaging
3 apparatus to image at least one anatomical marker and using such image to guide
4 the positioning of catheter such that the penetrator will enetr the desired location
5 of the myocardium.

1 213. A method according to Claim 212 wherein the imaging apparatus is an
2 ultrasound imaging apparatus and the image used in Step C is an ultrasound
3 image.

1 214. A method according to Claim 211 wherein the guidance element comprises
2 indicia that indicates the path that will be followed by the penetrator when it is
3 subsequently advanced from the catheter and wherein Step C further comprises
4 obtaining an image of the imageable marker and using such image to guide the
5 positioning of the penetrating catheter.

1 215. A method according to Claim 211 wherein the guidance element comprises
2 the combination of an imaging apparatus and at least one imageable marker on the
3 penetrating catheter, and wherein Step C further comprises using the imaging
4 apparatus to obtain an image of at least the imageable marker and using that
5 image to guide the positioning of the penetrating catheter.

1 216. A method according to Claim 215 wherein the imageable marker provides
2 an indication of the direction in which the penetrator will advance and wherein Step
3 C further comprises imaging of the imageable marker to obtain an indication of the
4 direction in which the penetrator will advance and using said indication to

5 rotationally orient the penetrating catheter such that subsequent advancement of
6 the penetrator will cause the penetrator to travel in the direction of a desired
7 intramyocardial site.

1 217. A method according to Claim 211 wherein the guidance element comprises
2 an emitter located on or in the catheter body, said emitter emitting a signal that is
3 received by an extracorporeally situated signal-receiving apparatus and wherein
4 Step C further comprises using an extracorporeally situated signal-receiving
5 apparatus to receive a signal from the emitter and to thereby guide the placement
6 of the penetrating catheter.

1 218. A method according to Claim 203 wherein the system provided in Step A
2 further comprises a guide catheter through which the penetrating catheter is
3 advanceable and wherein, prior to performance of Step B, the method further
4 comprises the step of:

5 inserting the guide catheter into the patient's vasculature and advancing the
6 guide catheter to a location within a chamber of the heart, and,
7 wherein Step B further comprises inserting the tissue penetrating catheter
8 into the patient's vasculature and advancing the tissue penetrating catheter through
9 the guide catheter to a position where the location on the tissue penetrating
10 catheter from which the tissue penetrator advances is located within a chamber of
11 the patient's heart.

1 219. A system according to Claims 1 or 126 wherein the delivery catheter further
2 comprises a position indicator for indicating the position of the delivery catheter
3 within tissue.

1 220. A system according to Claim 219 wherein the position indicator comprises
2 a radiographically visible marker.

- 1 221. A method according to Claims 61 or 202 wherein the delivery catheter further
2 comprises a position indicator for indicating the position of the delivery catheter
3 within tissue and wherein the method further comprises the step of:
4 using the position indicator to discern the position of the delivery catheter
5 within the patient's body at at least one time during the procedure.

- 1 222. A method according to Claim 221 wherein the position indicator comprises
2 a radiographically visible marker and wherein the step of using the position indicator
3 to discern the position comprises using a radiographic imaging apparatus to discern
4 the location of the radiographically visible marker.

- 1 223. A method according to Claims 61 or 202 wherein the method comprises
2 advancing a delivery catheter through the penetrator and injecting a substance
3 though the delivery catheter.

- 1 224. A method according to Claim 223 wherein the method further comprises
2 moving the delivery catheter while injecting the substance.

- 1 225. A method according to Claim 224 wherein the delivery catheter is advanced
2 while injecting the substance.
- 1 226. A method according to Claim 224 wherein the delivery catheter is retracted
2 while injecting the substance.

- 1 227. A method according to Claim 224 wherein the substance is injected
2 continuously while the delivery catheter is moved to deposit the substance over an
3 elongate area or deposition.

- 1 228. A method according to Claim 224 wherein boluses of the substance are
2 injected at different times while the delivery catheter is moved to provide a plurality
3 of discrete deposits of the substance at different locations on the path over which
4 the delivery catheter was moved.

- 1 229. A method according to Claims 61 or 202 further comprising the steps of:
2 obtaining a quantity of tissue or cellular matter for use as a tissue graft; loading the
3 tissue graft into the delivery catheter; advancing the delivery catheter to an
4 interstitial site; and, delivering the tissue graft through the delivery catheter to the
5 interstitial site.
- 1 230. A method according to Claims 61 or 202 wherein a delivery catheter is
2 advanced through the penetrator and to a location adjacent to an anatomical cavity,
3 chamber or structure that the operator does not wish to penetrate with the delivery
4 catheter and, wherein at least one of the penetrator and delivery catheter are of
5 curved configuration such that the delivery catheter will advance through tissue on
6 a path of advancement that is not directed into the anatomical cavity, chamber or
7 structure that the operator does not wish to penetrate.
- 1 231. A method according to Claim 230 wherein the delivery catheter is advanced
2 into myocardial tissue adjacent to a chamber of the heart and at least one of the
3 penetrator and delivery catheter are of a curved configuration that causes the
4 delivery catheter to be advanced on a path of advancement that is generally
5 tangential to the adjacent chamber of the heart, the delivery catheter being thereby
6 advanced into the myocardial tissue without entering the chamber of the heart.

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Fig. 1

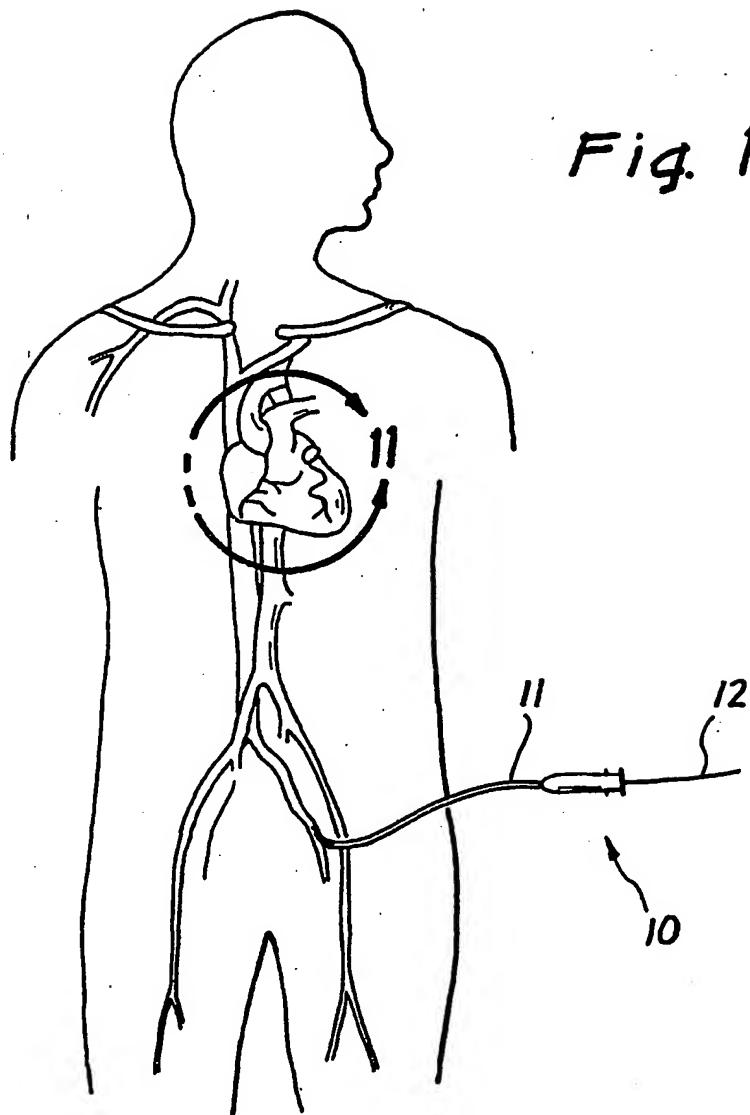
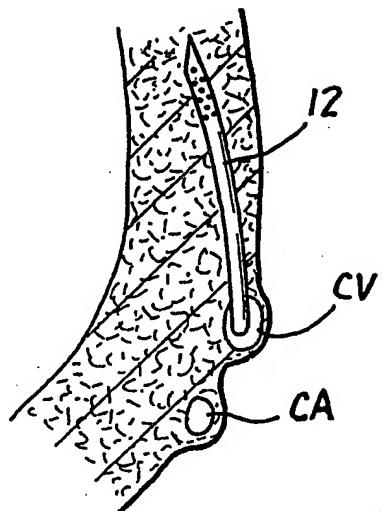


Fig. 10A



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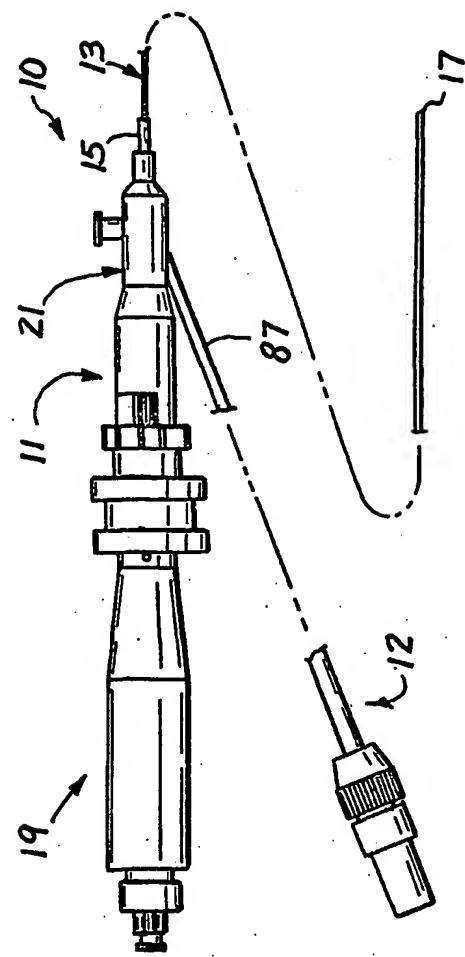
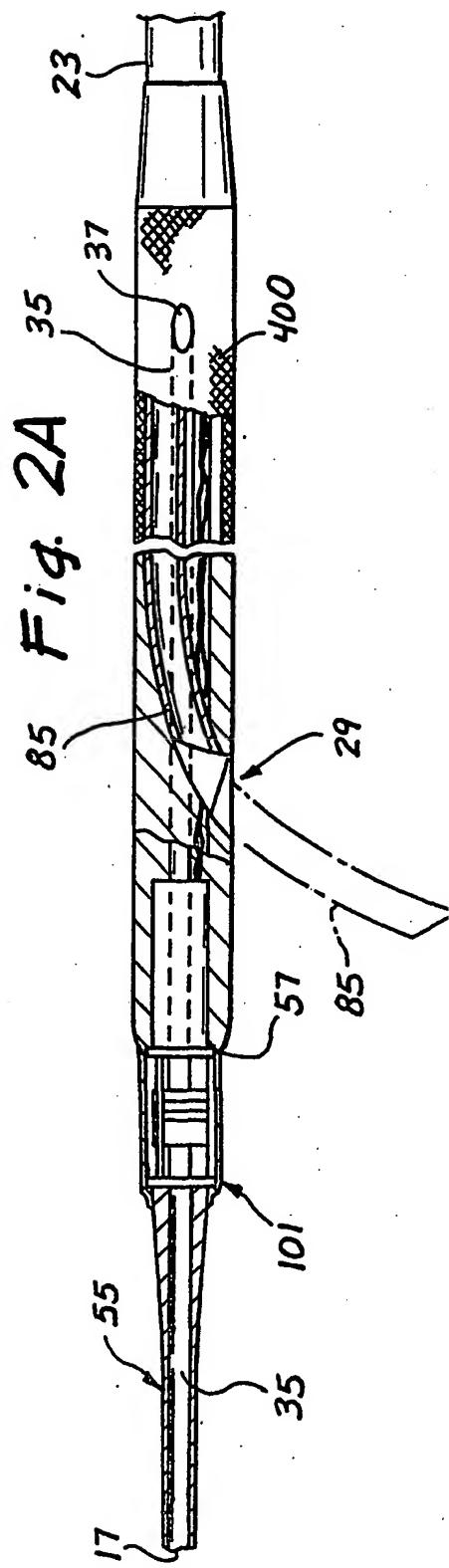
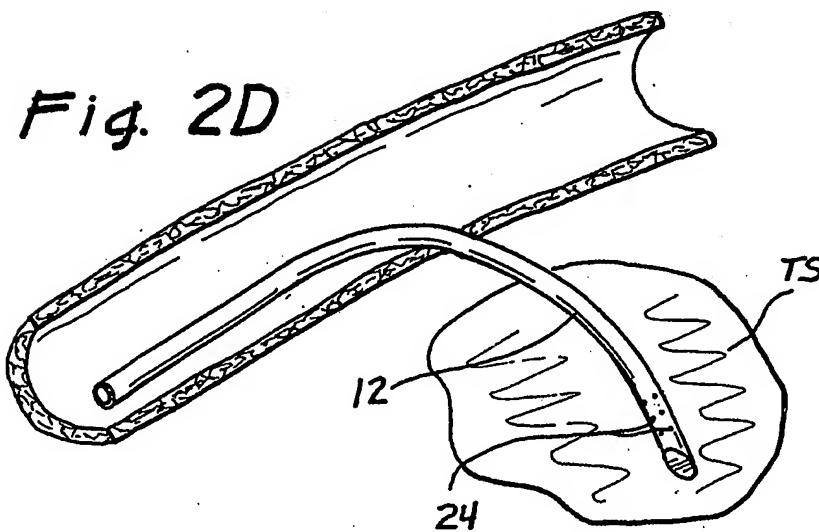
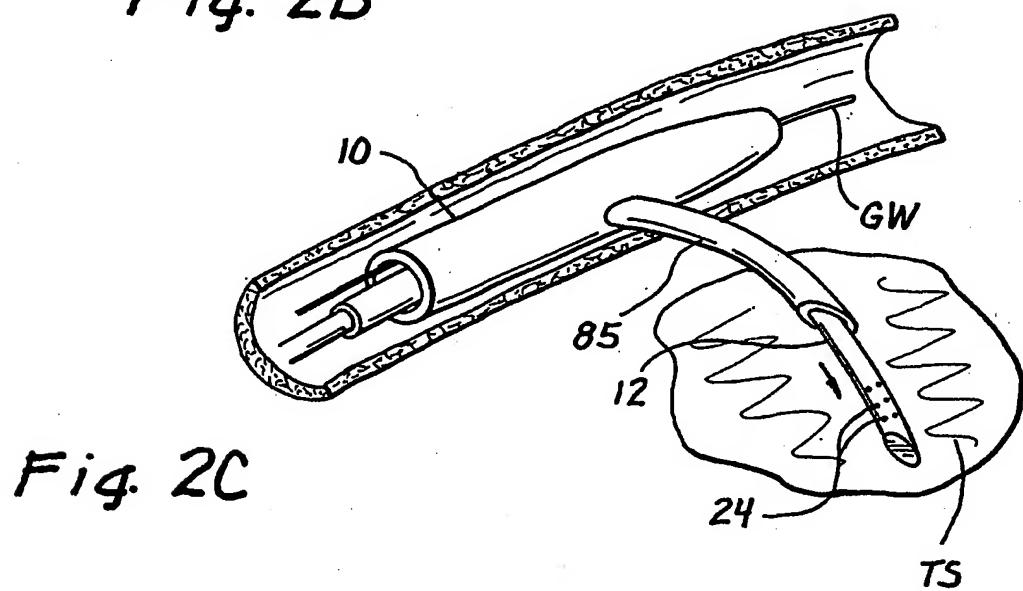
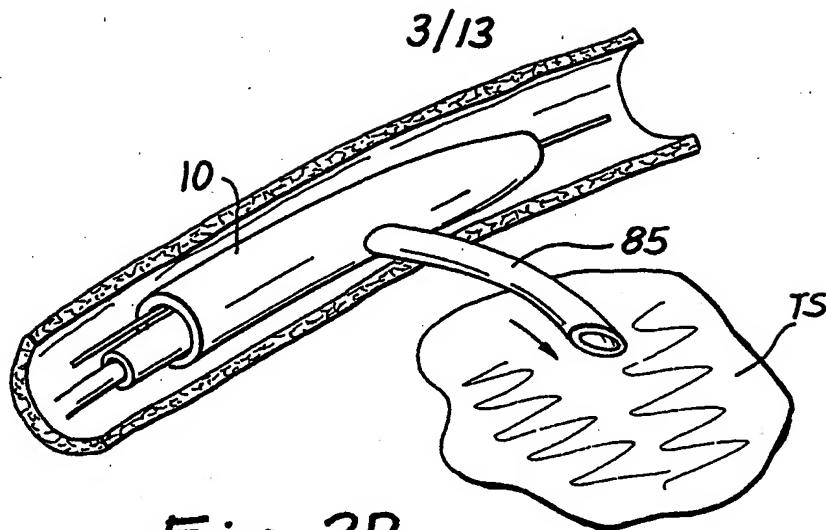


Fig. 2





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Fig. 3A

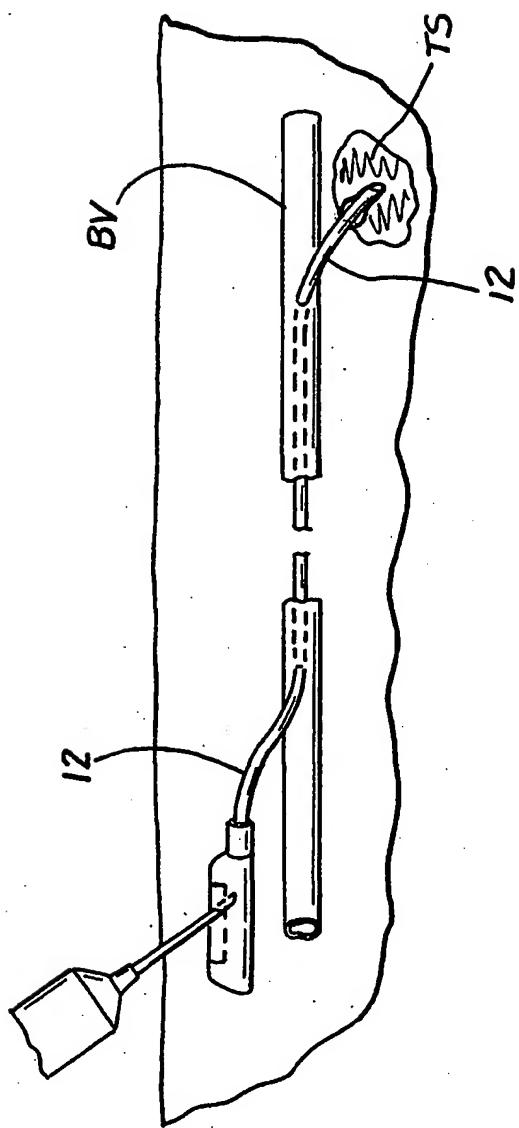
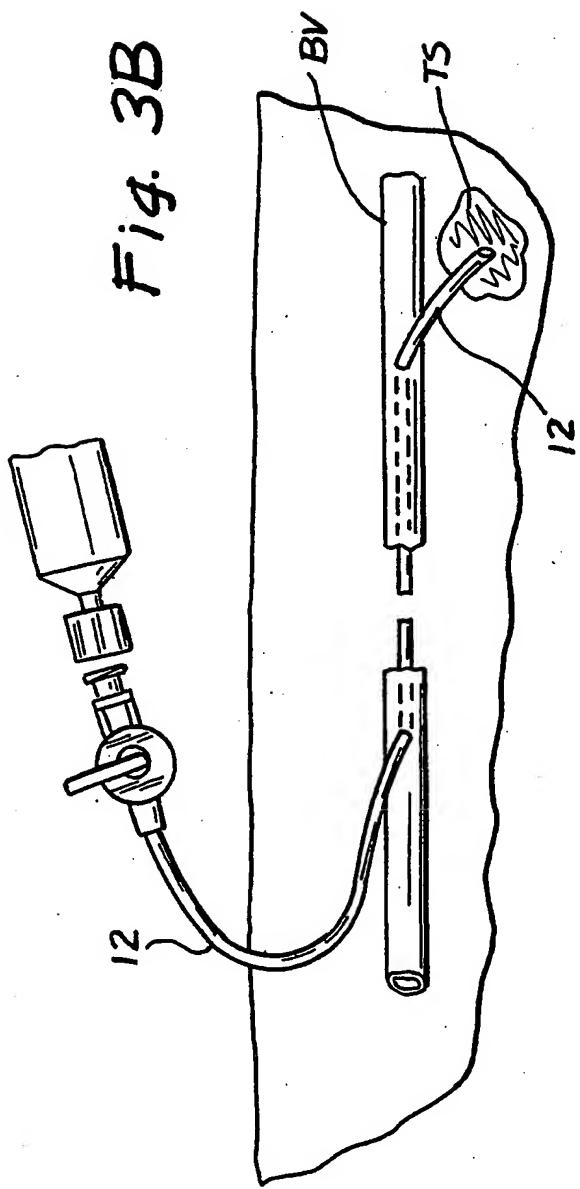


Fig. 3B



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Fig. 4

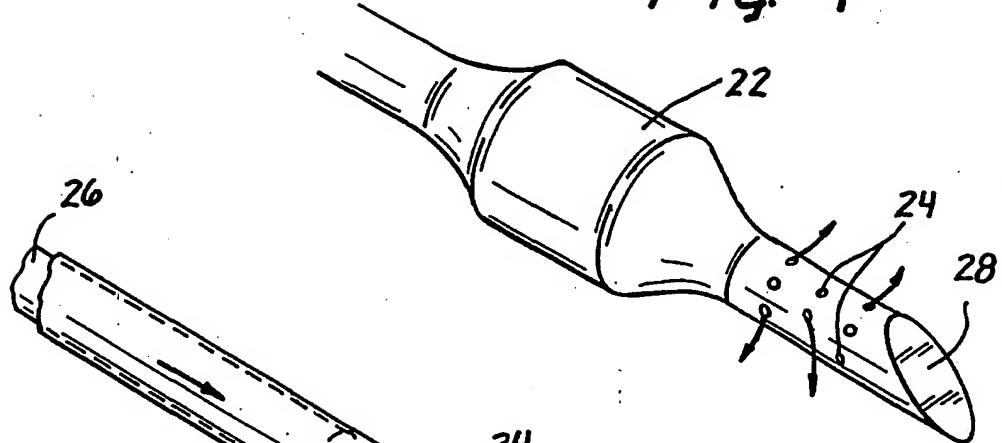


Fig. 5

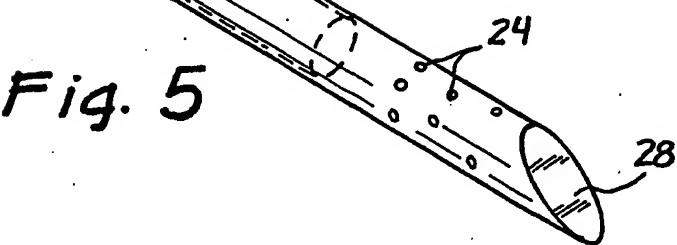


Fig. 6A

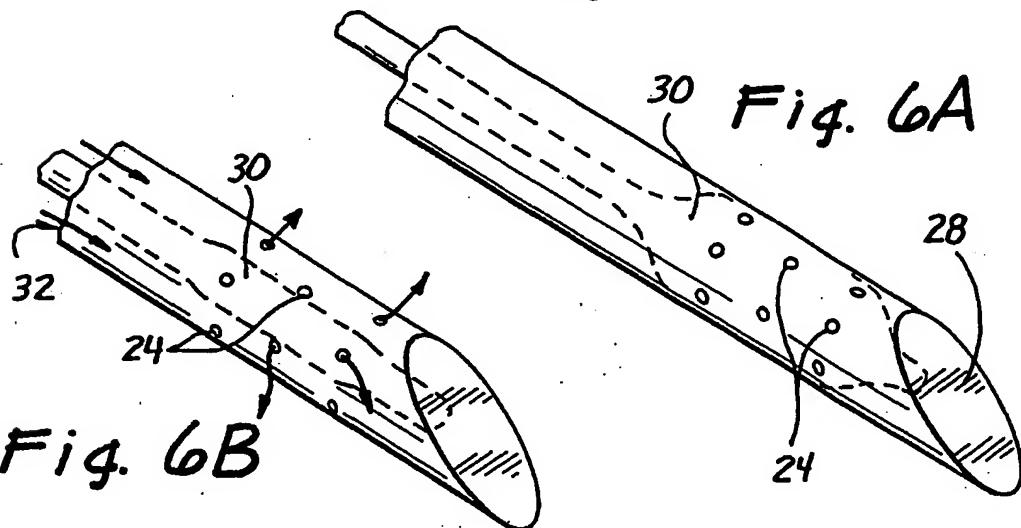
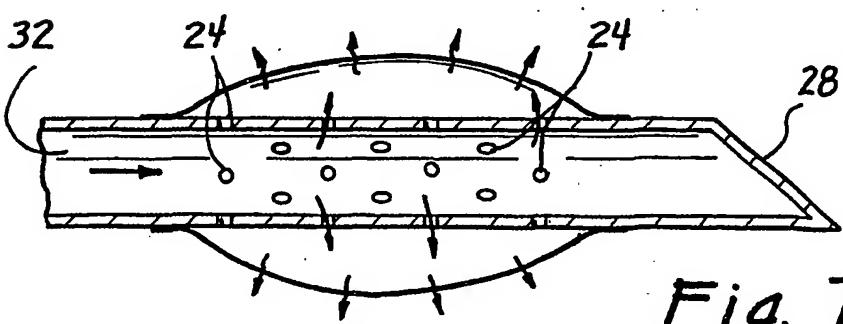


Fig. 6B



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Fig. 8A

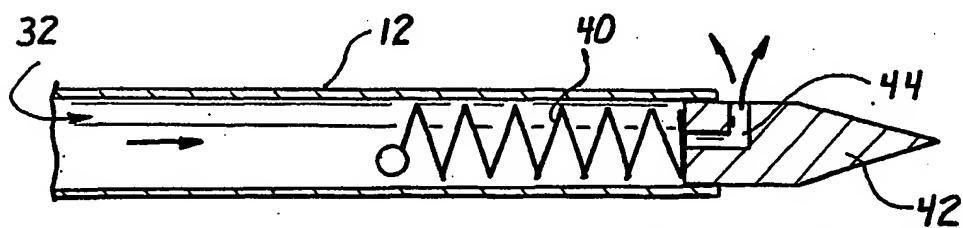
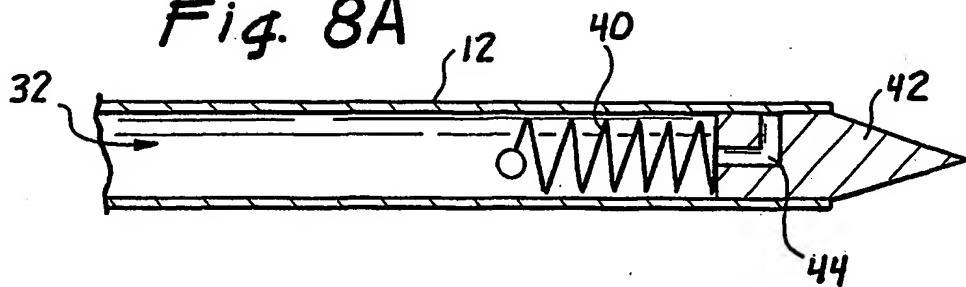
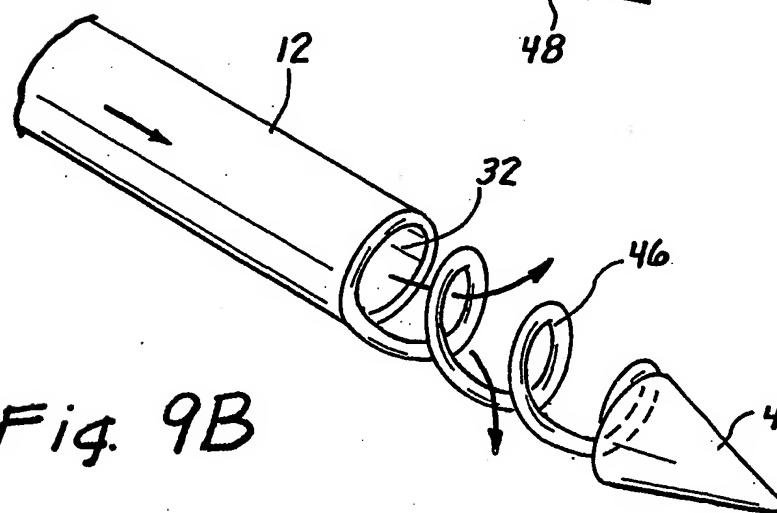
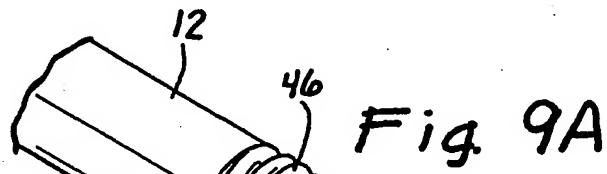


Fig. 8B



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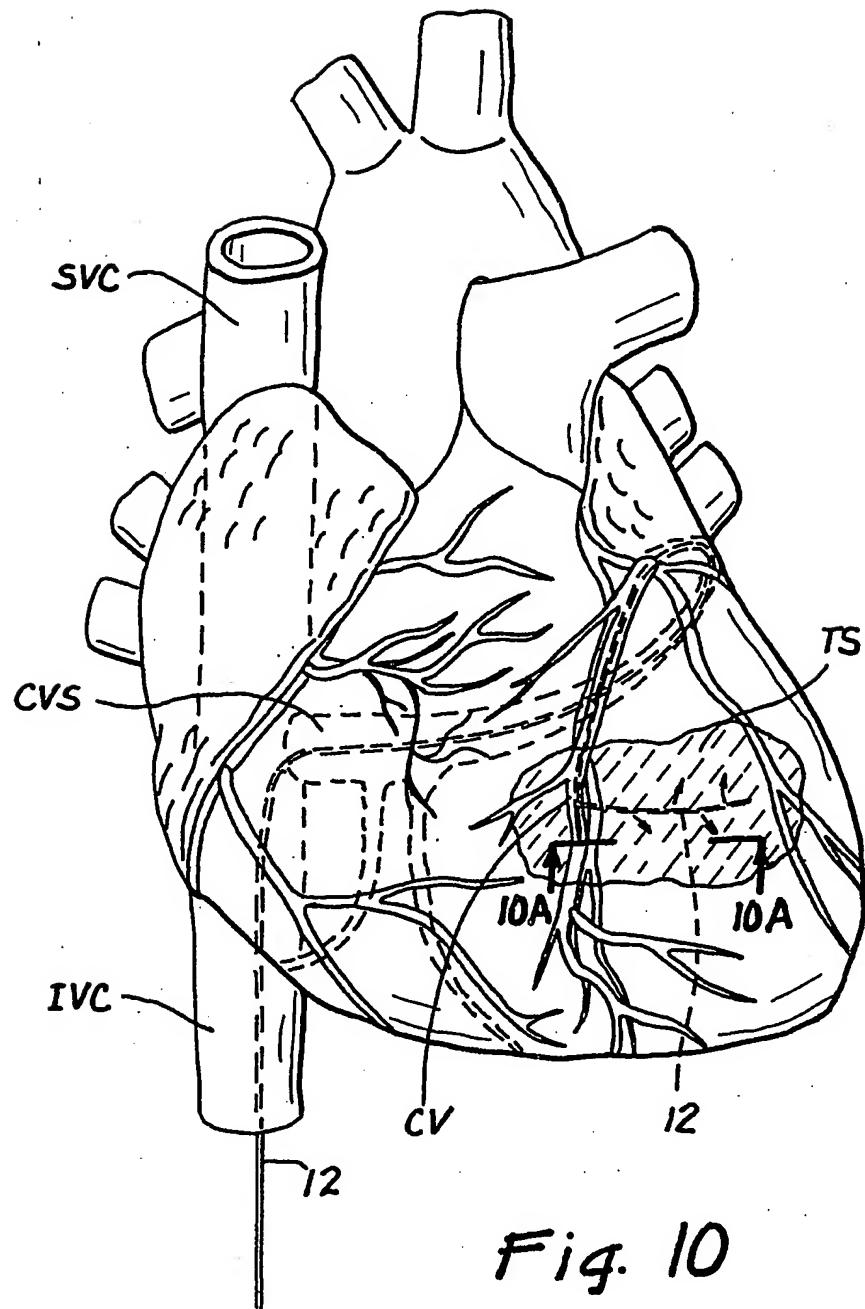


Fig. 10

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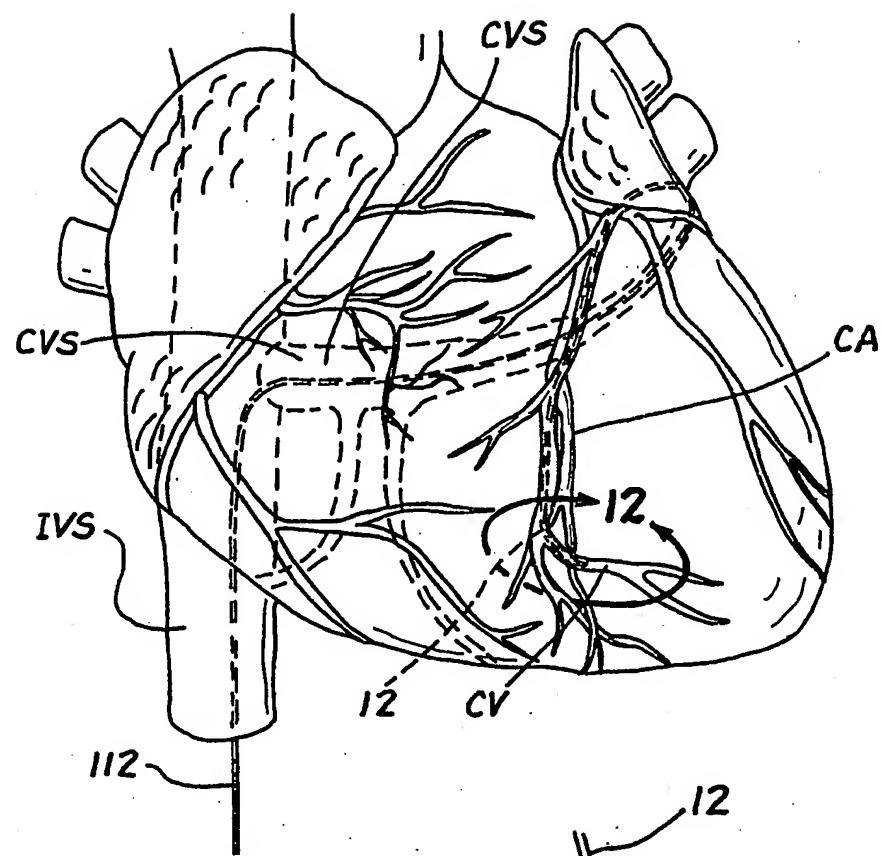
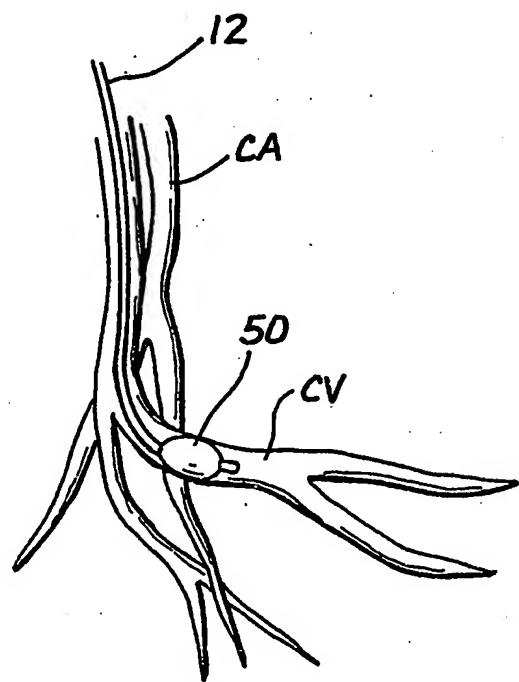


Fig. 11

Fig. 12



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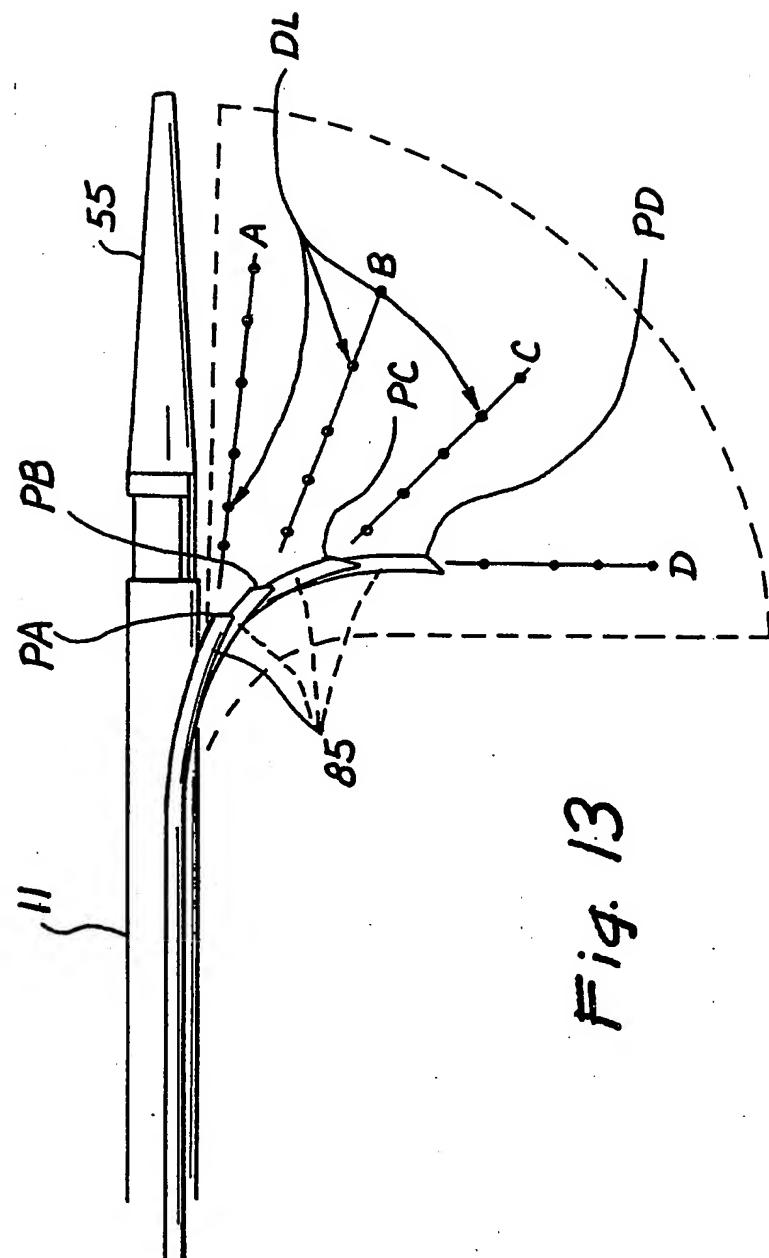


Fig. 13

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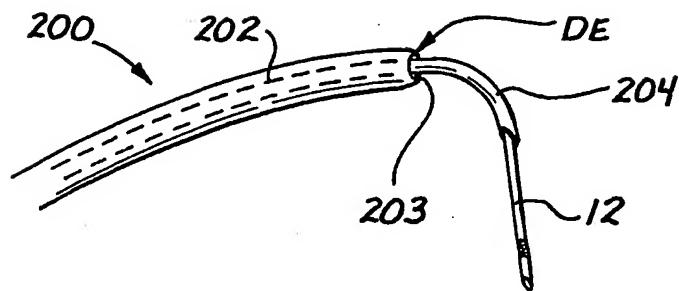


Fig. 14

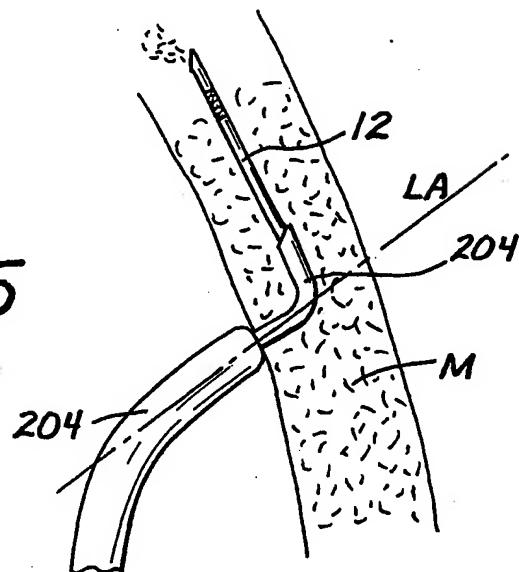


Fig. 15

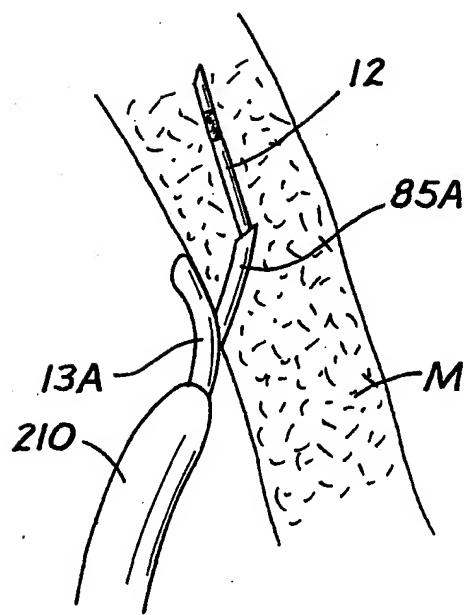


Fig. 17

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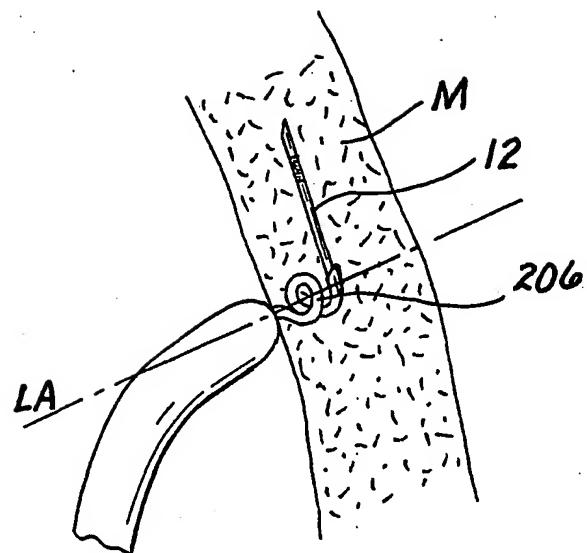
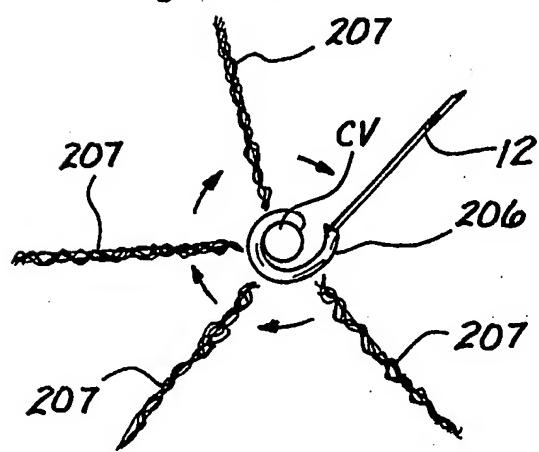


Fig. 16

Fig. 16A



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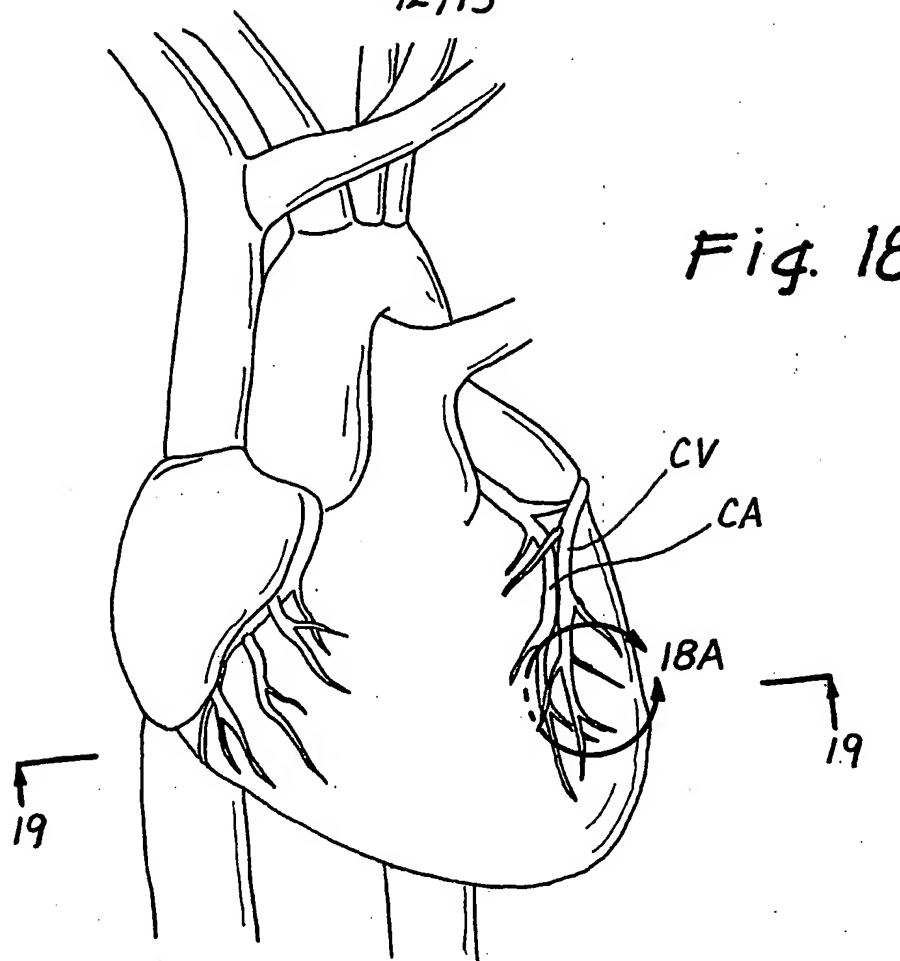
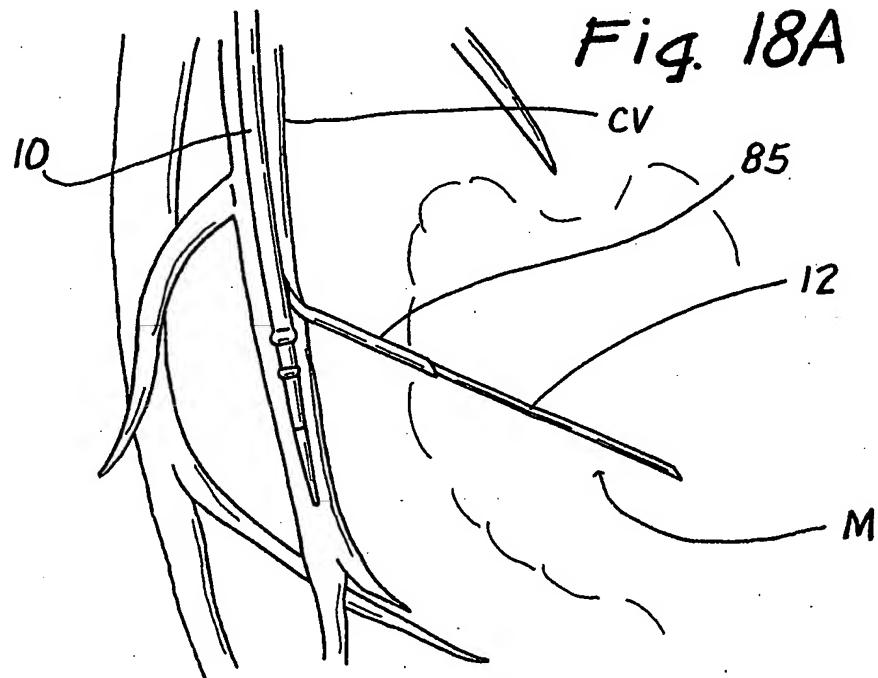


Fig. 18A



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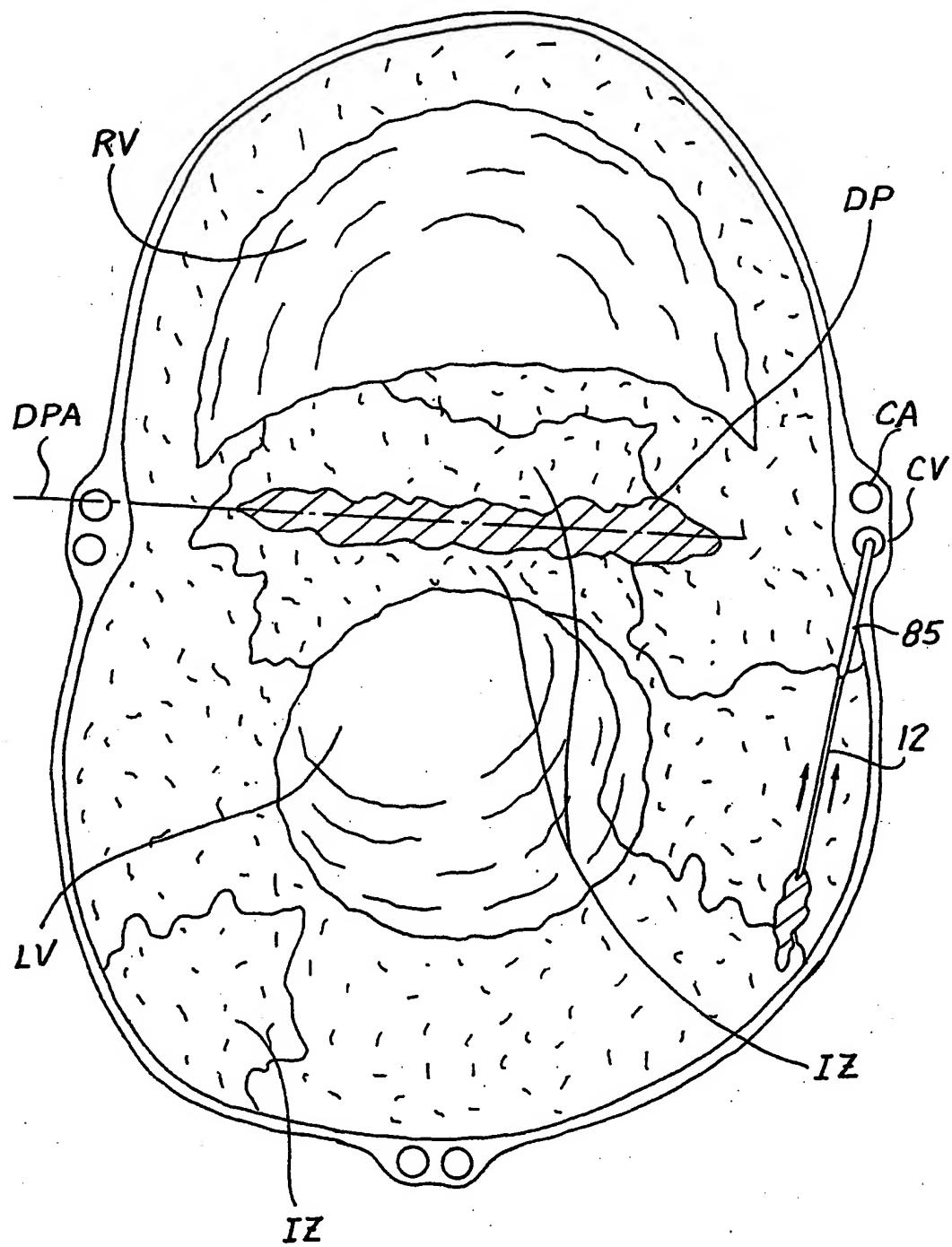


Fig. 19

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